A Textbook of

Preconceptional Medicine

and Management

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Edited by
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Foreword

A really comprehensive textbook on preconceptional medicine and management has been missing until now; however, it was obviously worth waiting for, because the book edited by our four colleagues Mahantesh Karoshi, Sandra Newbold, Christopher B-Lynch and Louis G. Keith fills this almost surprising gap in a unique way. All four editors are well known in different aspects of this important discipline of medicine, and they have carefully selected the authors of the Textbook so that a wide spectrum of subjects is covered which ranges from folate prohylaxis in, and especially before, pregnancy, to prevent neural tube defects in the child, by one of the Editors Louis G. Keith, to preconceptional optimization in solid organ recipients, by Sandra Jones and Sue Carr.

The essence of preconceptional counseling is different from the common principles of pregnancy care, as is elegantly pointed out by Rahat Khan and Hassan Shehata in their general chapter. They define the scope of preconceptional care as 'covering interventions that aim to identify and modify biochemical, behavioral and social risks to women's health or pregnancy outcome through prevention and management.' Logically, therefore, the first section of the book deals with the most important risk factors for women related to maternal age, heart disease, diabetes mellitus, endocrine, autoimmune and connective tissue disorders as well as kidney diseases, thrombophilic, inflammatory and neurologic disorders, hypertension and mental illnesses. The texts provide an excellent source of reference for any health care professional as do the subsequent sections of the book on infectious conditions, previous pregnancy events and phobias.

The topics are covered in a very didactic and sometimes even in an almost dialectic way. For example, the two chapters related to medication issues, the one on 'Routine vitamin, mineral and micronutrient supplementation' on the one side and that on 'Drugs to be avoided' on the other, both illustrate from opposite points of view how critical certain gestational age windows are for the undisturbed development of a child *in utero*, a lesson that was brought home in a dramatic way by the thalidomide catastrophe at the beginning of the 1960s which established the concept of the 'sensitive periods' during pregnancy for negative (i.e. teratogenic) and, as we now know equally well, also positive influences (i.e. periconceptional folate supplementation) on the development of the unborn child. Most often pregnancy care starts only after 10–14 menstrual weeks when the most sensitive and vulnerable period for the embryo has already passed, and this is why periconceptional counseling is so important.

Today, more and more often pregnancies are possible after treatment of gynecological and surgical conditions, but the preconceptional aspects of these circumstances have, to date, often been underestimated in their importance for an overall good outcome.

No book on preconceptional counseling would be complete without dealing at appropriate length and depth with the phenomena, sometimes even called epidemics, of obesity and malnutrition, and in the final section the book discusses these issues in an impressive way on a truly international scale.

A Textbook of Preconceptional Medicine and Management underlines in a scholarly and very practical way that the old English proverb is still true that 'An ounce of prevention is better than a pound of cure', but since this is a very up to date and truly international text you will forgive me for paraphrasing the original wisdom into a more modern phrasing: 'A microgram of prevention is better than a kilogram of cure. '

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SECTION 1
General considerations

1

Biopanic, advanced maternal age and fertility outcomes

Larisa Corda, Amita Khanapure and Mahantesh Karoshi

BIOPANIC

Although obesity and smoking are the most obvious public health effects of the numerous social changes occurring in the late 20th and early 21st centuries, a new epidemic is extending across the Western world and leading to a considerable burden on health resources as well as enormous personal suffering. This new scourge is that of aging motherhood. In modern society, the pressure of achieving financial, career and relationship fulfillments, whilst ensuring a spontaneous conception, which has least impact on the conceptus, optimum pregnancy outcome and a capacity to withstand demands of the baby and child, has led to the coining of the term 'biopanic'.

Importance of biopanic

Whereas less than 5% of women below the age of 25 fail to conceive naturally, this rate increases to 30% after the age of 35[1]. Moreover, the likelihood of a successful response to ovarian stimulation resulting in egg retrieval decreases as the woman ages and this, compounded by the fact that older women have a poor ovarian response, makes women aged 35 years or older less than ideal candidates for *in vitro* fertilization (IVF)[2]. For example, the embryo implantation rate is around 6% for women over 40, with a live birth rate around 3.5% in those aged over 45, and a cumulative live birth rate of 14.4% after five IVF attempts in women over 40 in contrast to 45% for those under age 35. Diminished embryo implantation combined with the steep rise in the rate of miscarriage account for the substantial decline in fertility noted after the age of 45[3–6]. According to the UK Office of National Statistics (Figure 1), over the past several years the largest increase in conception rates has occurred in women aged 40 and over, and this trend has persisted with no sign of decline. However, this change is juxtaposed against the biological irony of a significant reduction in fertility after the age of 35, which clearly cannot change[8].

The same picture holds true for the USA, which also has seen a remarkable shift in the

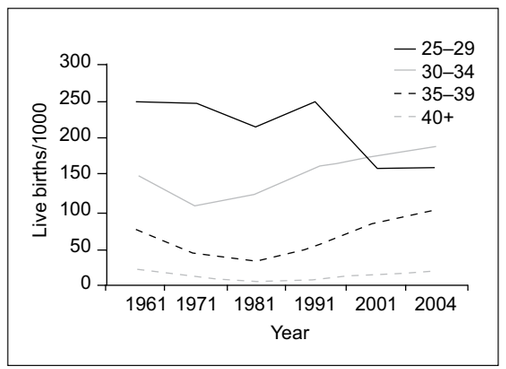

Figure 1 Maternal age groups at childbirth in England and Wales, 1961–2004. (Office for National Statistics, UK[7])

demographics of childbearing. The number of first births per 1000 women 35–39 years of age increased by 36% between 1991 and 2001, and the rate among women 40–44 years of age rose by a remarkable 70%[9]. The average age of women seeking IVF treatment according to the Human Fertilisation and Embryology Authority (HFEA) of the UK has risen in the 14 year interval between 1992 and 2005 from 33.8 years to 34.9 years, respectively, as is shown in Figure 2[10].

The age of menarche has decreased over generations, and life span has increased, but the age of the menopause has remained unchanged. The loss of female gametes with age is both quantitative and qualitative. The sense of urgency to conceive in the time when the number of gametes available is likeliest to result in a successful spontaneous pregnancy with a low chance of chromosomal abnormalities, and without encountering any obstetric or medical complications, is a pressure felt by a large number of women in modern day society. At the same time as they are pursuing their career, they desire to achieve successful pregnancy outcomes which creates a situation of 'biopanic'.

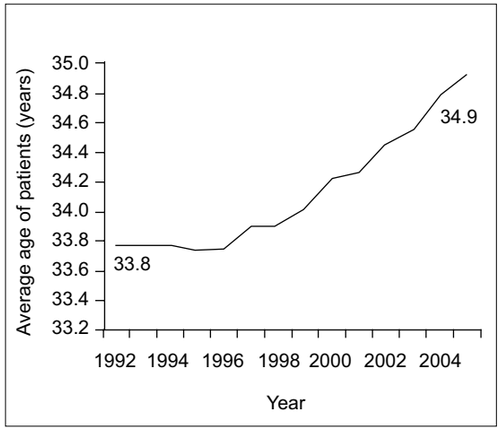

Figure 2 Trends in average age of patients requesting *in vitro* fertilization 1992–2005. (Reproduced with permission from Human Fertilisation and Embryology Authority[10])

ADVANCED MATERNAL AGE

Advanced maternal age (AMA) is defined as age 35 or more for the mother at the time of delivery of her baby.

Advanced maternal age predisposes to Down's syndrome (trisomy 21). The risk of having a Down's syndrome baby rises with maternal age, essentially doubling from 1 in 725 at maternal age 32 to 1 in 365 at maternal age 35. This risk continues to climb and is 1 in 32 at maternal age 45.

Importance of advanced maternal age

The effect of maternal age on the outcome of pregnancy may be best assessed by examining specific factors that can negatively affect the desired outcome of a pregnancy: declining fertility, miscarriage, chromosomal abnormalities, hypertensive complications, stillbirth and maternal mortality.

Fertility rate and maternal age at conception

Figure 3 shows the effect of maternal age on the average rate of pregnancy, calculated on the basis of ten different populations living between the 17th and 20th centuries that did not use contraceptives. Fertility remains relatively stable through to 30 years of age, at more than 400 pregnancies per 1000 exposed women per year, and then begins to decrease substantially. By 45 years of age, the fertility rate is only 100 pregnancies per 1000 exposed women[11]. Figure 4[9] and Table 1[12] depict the effect of age on the spontaneous miscarriage rate.

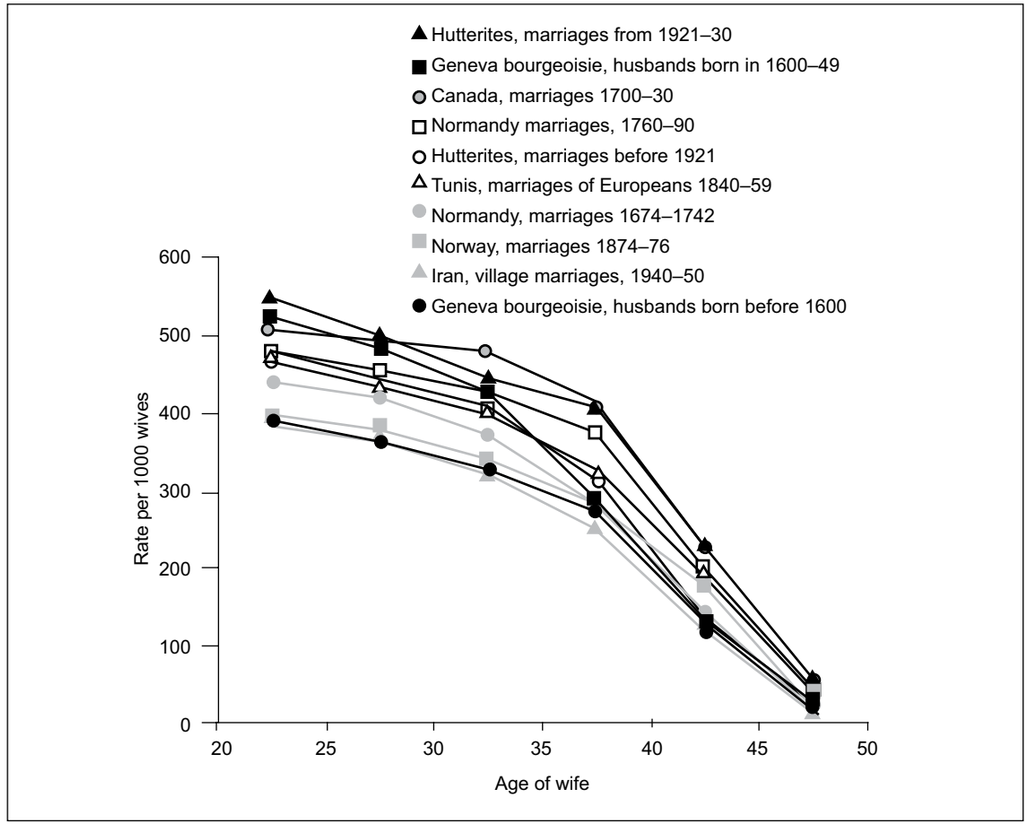

Figure 3 Fertility rates and advanced maternal age. (Reproduced from Menkel *et al*., 1986[11], with permission from American Association for the Advancement of Science)

Reproductive issues

Fertility, defined as the natural ability of a woman to reproduce, declines gradually over the woman's life span[13]. Although this decline seems to begin at about age 30, it is more obvious between 35 and 40, and increases dramatically thereafter. The possibility of a spontaneous pregnancy occurring is less than 2% around the age of 42 and almost 0% after 45 years[14–17]. In actuality, fertility reaches its nadir after the age of 40. Thus, the overall contribution to the total number of births in a given population from 40-year-old women is 1%, and from 47-year-old women 0.01%[14]. The implantation rates also decline dramatically as menopause approaches, dropping from 20% at the age of 30 to less than 4% at the age of 40 years[13]. Accordingly, birth rates decrease significantly with advancing maternal age, presenting a drop of 95% at the age of 45, and of almost 100% around menopause[2,13,14]. However, age 41 is generally considered to be the point when fertility stops and subfertility starts. Therefore, menopause in reality occurs approximately 10 years after the substantial loss of conception potential[2,14] (Figure 5).

There are 4–7 million primary oocytes in the ovaries of a 20-week-old female fetus, but this number is halved at birth. By puberty there are

only 400,000 oocytes available in the ovaries, but only 400–500 eventually undergo ovulation[13]. From puberty onward, the loss of follicles is continuous throughout the woman's reproductive life (Figure 6). The phenomenon of oocyte depletion happens even under conditions of ovarian suppression, as is the case in pregnancy or with the use of combined oral contraceptives. The depleted oocytes undergo atresia through apoptosis or necrosis[18,19]. Because the ovarian pool of follicles declines exponentially with advancing age, from the age of 35 there is an accelerated loss of follicles, so that at 38, a woman may have only 25,000 follicles available, at age 40, 15,000, at age 45, her reserve may have declined to 5000, and in her early 50s, only a few hundred remain (Figure 6)[20]. Under these circumstances, IVF, a procedure selected by approximately 20% of

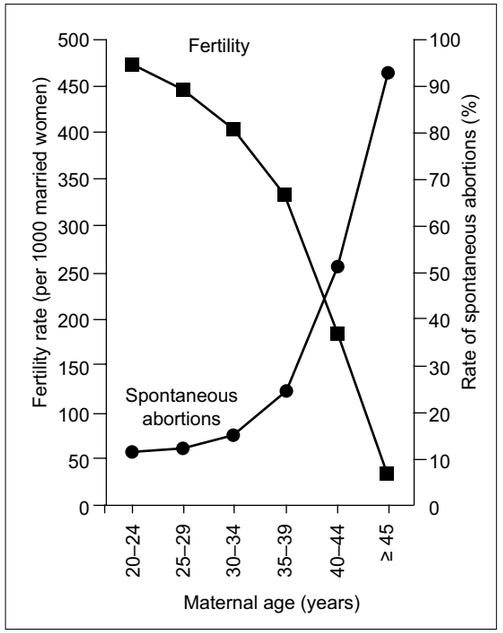

Figure 4 Fertility and miscarriage rates as a function of maternal age. (Reproduced from Heffner, 2004[9], with permission from Massachusetts Medical Society)

Table 1 Incidence of miscarriage by different age groups. (Reproduced from Madankumar *et al.*, 2003[12], with permission from Elsevier)

Maternal age (years)	*Miscarriage rates*
<19	10.3%
20–29	9.7%
30–34	11.5%
35–39	21.1%
40+	42.4%

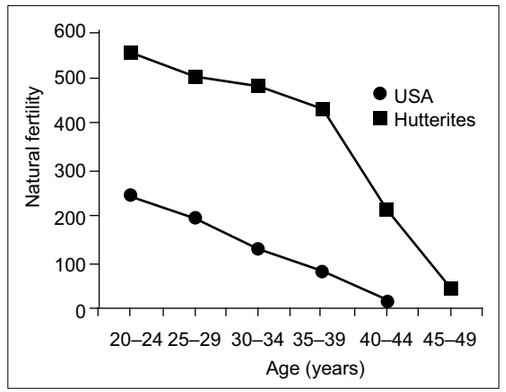

Figure 5 Natural fertility according to age in different populations

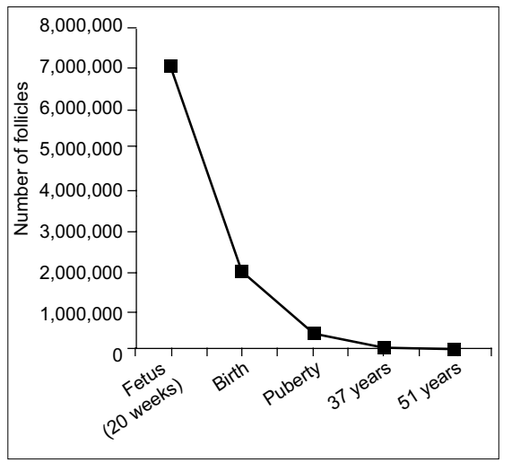

Figure 6 Number of follicles in the ovaries during a woman's life

women between the ages of 35 and 44 wishing to conceive, has a much less successful outcome with advancing age, as the number of gametes available is much lower (Table 2).

Compiled data from IVF programs since their inception show that whereas outcomes have improved for those aged under 35, no significant increase in those aged 35 and over has been seen. Moreover, the natural effect of biology on declining fertility is compounded by pathology, by which many older women have more time to accumulate detrimental medical conditions including diabetes and increased body mass index (BMI), which, although varying with age, are more common on average for older women, with trends being apparent through the childbearing years as shown in the Confidential Enquiries into Maternal and Child Health, 2007 (Table 3). Other accumulated conditions include sexually transmitted infections and their consequences, uterine fibroids, endometriosis, tubal damage, cervical disease and acquired thrombophilias, all of which can compromise fertility.

Table 4 shows the risks of Down's syndrome and any chromosomal abnormality according to 5-year increments of maternal age[24]. Advanced paternal age, which is frequently associated with advanced maternal age, increases the risk of autosomal dominant diseases, such as

Table 2 Pregnancy success rates in 2007. (Reproduced from Centers for Disease Control and Prevention, 2009[21], with permission)

	Age of women			
Type of cycle	*<35*	*35–37*	*38–40*	*41–42*
Fresh embryos from non-donor eggs				
Number of cycles	42,127	23,504	20,612	9535
Percentage of cycles resulting in pregnancies	45.7	37.2	28.1	18.4
Percentage of cycles resulting in live births	39.6	30.5	20.9	11.5
Percentage of retrievals resulting in live births	42.9	34.2	24.4	14.0
Percentage of transfers resulting in live births	45.9	36.9	27.1	16.0
Percentage of transfers resulting in singleton live births	29.9	25.7	20.6	13.6
Percentage of cancellations	7.6	10.8	14.1	17.8
Average number of embryos transferred	2.2	2.5	2.8	3.1
Percentage of pregnancies with twins	33.2	28.2	21.6	14.0
Percentage of pregnancies with triplets or more	3.5	4.5	4.0	2.5
Percentage of live births having multiple infants	34.9	30.4	23.9	15.4
Frozen embryos from non-donor eggs				
Number of transfers	10,518	5388	3518	1126
Percentage of transfers resulting in live births	33.6	29.9	25.0	20.9
Average number of embryos transferred	2.2	2.2	2.4	2.5

	All ages combined	
Donor eggs	*Fresh embryos*	*Frozen embryos*
Number of transfers	10,321	5633
Percentage of transfers resulting in live births	55.1	31.9
Average number of embryos transferred	2.2	2.3

Table 3 Trends in body mass index (BMI) expressed as percentage by age, England. (Reproduced from Confidential Enquiry into Maternal and Child Health, 2007[22], with permission)

	BMI					
Year	*18.5 or under*	*18.6–25.0*	*25.1–30.0*	*30.1–40.0*	*Over 40*	*All*
1993	1.9	49.5	32.2	15.0	1.4	100.0
1994	2.2	49.1	31.4	15.7	1.6	100.0
1995	2.2	47.4	32.9	16.1	1.4	100.0
1996	2.0	46.0	33.6	17.0	1.4	100.0
1997	1.9	45.6	32.8	17.4	2.3	100.0
1998	2.1	44.6	32.1	19.3	1.9	100.0
1999	1.8	44.3	32.8	19.2	1.9	100.0
2000	1.8	43.1	33.8	19.1	2.3	100.0
2001	1.6	41.9	32.9	21.0	2.5	100.0
2002	1.9	41.6	33.7	20.2	2.6	100.0
2003	1.9	41.3	33.4	20.6	2.9	100.0
2004	1.7	39.8	34.7	21.3	2.6	100.0
2005	1.6	40.7	32.9	19.0	2.9	100.0

Table 4 Risk of Down's syndrome and chromosomal abnormalities at live birth, according to maternal age[23]

Maternal age at delivery (years)	*Risk of Down's syndrome*	*Risk of any chromosomal abnormality*
20	1/1667	1/526
25	1/1200	1/476
30	1/952	1/385
35	1/378	1/192
40	1/106	1/66
45	1/30	1/21

achondroplasia and Marfan's syndrome, that appear to result from new genetic mutations[9].

It is not just defects resulting from chromosomal anomalies which are more prevalent in the offspring of the older age group, but also non-chromosomal congenital abnormalities such as cardiac defects, club foot, spina bifida, diaphragmatic hernia and limb defects[24]. Whereas the baseline risk of congenital malformation for women aged under 25 is around 3.5%, this risk increases by an additional 1% and 2.5% when the woman is over 35 and over 40, respectively[25].

Preimplantation genetic screening for aneuploidy

Preimplantation genetic screening (PGS) refers to techniques whereby certain categories of patient thought to be at a higher than average risk of conceiving chromosomally abnormal embryos have their embryos tested (by blastomere or polar body biopsy) to determine whether specific abnormalities are present.

The purpose of preimplantation screening for aneuploidy is to help those seeking assisted conception treatments for infertility to achieve a successful pregnancy and to reduce their risk of miscarriage. Whilst it helps to identify chromosomally abnormal embryos, aneuploidy screening (PGS) does not necessarily identify normal embryos. In some cases, information

discovered through preimplantation testing may help those who have been unable to conceive to identify the underlying basis of their infertility.

It is anticipated that PGS for aneuploidy has a role in the treatment of the following categories of patient:

1. Women over 35 years of age;
2. Women with a history of recurrent miscarriage not caused by translocations or other chromosomal rearrangements;
3. Women with several previous failed IVF attempts where embryos have been transferred[10].

All the above, either alone or in combination, may be present in patients with AMA.

Medical disorders associated with advanced maternal age

Hypertension

The incidence of pregnancy induced hypertension is doubled by the time a woman reaches 35, compared to its incidence in the preceding decade[26]. This fact, along with the observed reduction in arterial compliance seen with aging, accounts for the increased incidence of cardiovascular disease in older gravidas, as well as the increased morbidity and mortality affecting this age group[27].

Vascular reserve capacity is likely to be compromised by the increased prevalence of chronic hypertension in older age. Compared to controls, chronic hypertension is increased fivefold in older nulliparas and ninefold in older multiparas[28]. Pre-eclampsia may complicate chronic hypertension which then results in complications, such as fetal growth restriction and placental abruption[29]. The rate of pre-eclampsia in women aged over 35 was almost three times that in younger women, this being a direct consequence of a greater preponderance of hypertensive disease in the older age group[30]. If pre-eclampsia does occur, it is likely to be severe[31].

Diabetes

The incidence of type 2 diabetes increases with age. This condition is a state of relative insulin deficiency which results because of either a reduced production of insulin from the pancreatic islet cells or a reduced sensitivity to the effects of insulin within the body. Both phenomena decline as aging proceeds[32]. With older age, the production of insulin is diminished[33]. Up to 16% of women of AMA have a positive glucose tolerance test. The increase in gestational diabetes amongst older mothers may be due to progressive endothelial damage or to the onset of obesity, also observed in this group[34].

Obstetric issues

The increased occurrence of uterine fibroids can lead to obstetric complications such as placental abruption, fetal malpresentation and dysfunctional labor[35].

Women aged more than 40 years have a poor chance of a successful pregnancy, irrespective of their reproductive history. A large scale study from Denmark over a period of 15 years (1978–1992) involving a total of 634,272 women and 1,221,546 pregnancies demonstrated that the overall risk of fetal loss was 13.5%. The risk of fetal loss according to maternal age at conception followed a J-shaped curve, with a steep increase after 35 years of age (Figure 7). More than one-fifth of all pregnancies in 35-year-old women resulted in fetal loss, and at 42 years of age more than half of intended pregnancies (54.5%) resulted in fetal loss. The risk of spontaneous abortion varied from a minimum of 8.7% at the age of 22 years to 84.1% by the age of 48 years or more[36].

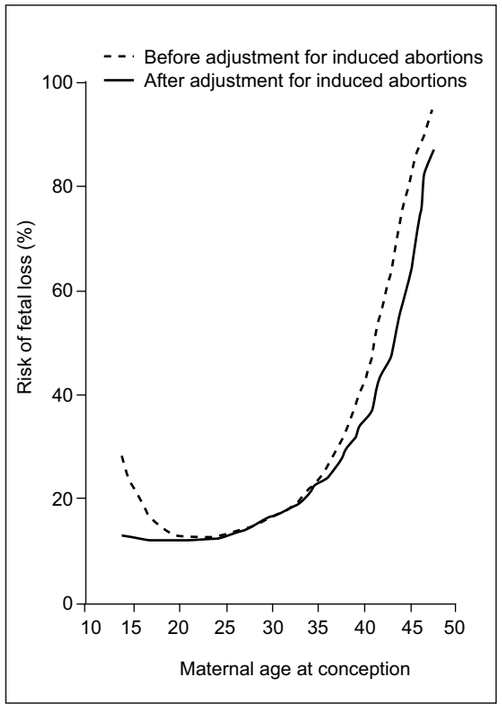

Figure 7 Risk of fetal loss from spontaneous abortion, ectopic pregnancy and stillbirth according to maternal age at conception. (Reproduced from Nybo Andersen *et al.*[36], with permission from BMJ Publishing Group Ltd)

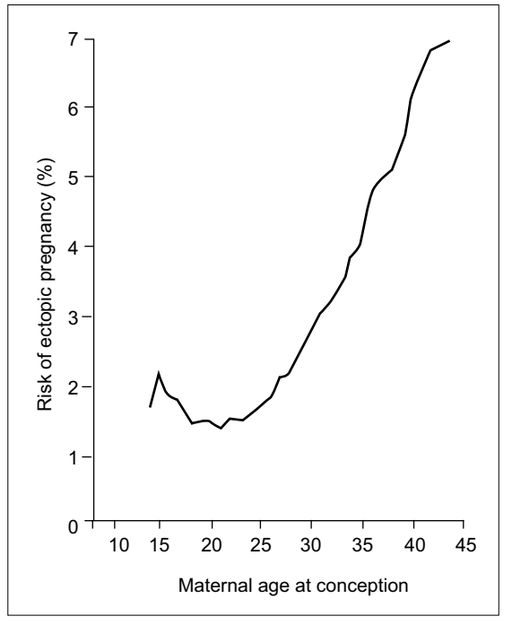

Figure 8 Risk of ectopic pregnancy rate according to maternal age. (Reproduced from Nybo Andersen *et al.*[36], with permission from BMJ Publishing Group Ltd)

It is difficult to understand the effect of age alone on the rate of miscarriage, as multiple confounding factors are involved, including chromosomal alterations, reduced fertility, coexisting disease and a greater number of conceptions initiated by assisted reproductive techniques.

The incidence of ectopic pregnancy showed a steady increase with increasing maternal age at conception from 1.4% of all pregnancies at the age of 21 years to 6.9% of pregnancies in women aged 44 years or more[36] (Figure 8). This change may be secondary to an increased prevalence of risk factors such as sexually transmitted and pelvic inflammatory disease or due to the effect of reducing tubal motility with increasing age.

A few studies have shown a lower mean gestational age at delivery in older women, with an increased incidence of preterm delivery at under 28 and 32 weeks of gestation[37]. Increasing maternal age shows an association with intrauterine growth restriction[38,39]. Figure 9 shows the association of AMA and adverse perinatal outcomes.

Stillbirth rate

Whereas women under the age of 30 have the lowest rate of fetal death, this rate increases with advancing maternal age, with women age 40 or older having twice the fetal death rate of women younger than 30 (Figure 10)[40]. Although the absolute rate of fetal death has

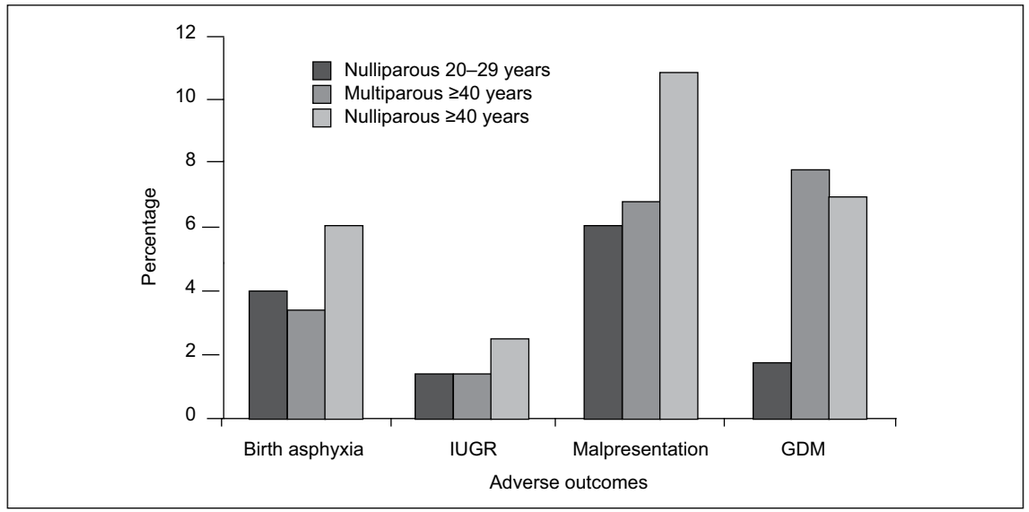

Figure 9 Adverse outcomes associated with advanced maternal age and parity. IUGR, intrauterine growth retardation; GDM, gestational diabetes mellitus. (Data from Gilbert *et al.*[28])

declined significantly for women of all age and parity groups since 1968 as compared to 1978, older women nevertheless remain at higher risk for fetal death, even after controlling for common diseases associated with older age, such as diabetes and hypertension, and complications of pregnancy such as abruption, all of which are also associated with increasing maternal age. Exactly why AMA is an independent risk factor for fetal death remains unexplained.

The increased incidence of obstetric complications is intimately associated with the incidence of cesarean section, which is far greater in women who are older[41,42]. Women aged 35 and over are 1.5 times more likely to undergo operative delivery compared to their younger counterparts[31]. Primary reasons include fetal distress, malpresentation secondary to pelvic pathology, and protracted labor. The latter is thought to be as a result of an age related decline in myometrial gap junction deficiency or a reduced sensitivity of myometrial oxytocin receptors[34,43]. In addition, an age related decline in pelvic elasticity[44,45] and myometrial

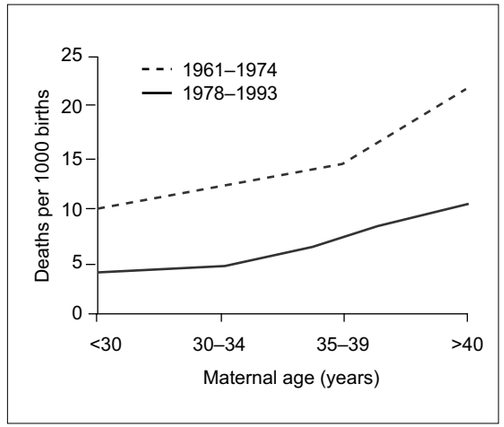

Figure 10 Increased maternal age and the risk of fetal death. (Reproduced from Fretts *et al.*[40], with permission from Massachusetts Medical Society)

function of the reproductive tract, along with fibrosis of the myometrial arteries, make normal vaginal delivery more difficult in older women and contribute to the prevalence of operative deliveries[44–46]. According to some reports, cesarean section rates in women aged

over 35 range between 21% and 52% (Figure 11)[26,28,47].

Cesarean rate and advanced maternal age

The concept of having a 'premium baby', the higher incidences of abruptio placentae, placenta previa, preterm labor, multiple pregnancy and malpresentation, as well as the widely held personal conviction that the index pregnancy may be the last chance to achieve a successful pregnancy, act in isolation or in combination and contribute to the excessive cesarean rate observed in the AMA group. Other factors also are operational, including induction of labor especially if the pregnancy exceeds 41 weeks[46], and antepartum hemorrhage from either placental abruption or placenta previa[34]. This latter risk is substantially greater with a 23% increase of placental abruption in women aged 35–49, in particular those with twin pregnancies, compared to pregnancies in women of younger age, although the risk of placenta previa in older nulliparous women is lower (around eight times higher than the baseline risk)[28].

Neoplastic disorders associated with maternal age

The older mother also runs a risk of developing certain cancers if she delays childbearing until a later age[48] (Figure 12), and numerous reports document AMA women becoming pregnant whilst being investigated or treated for cancerous conditions. To avoid the effects of radiation and cytotoxicity on embryo/fetus, it is crucial to offer effective contraception and also to make the patient aware of its availability. The commonly encountered cancers

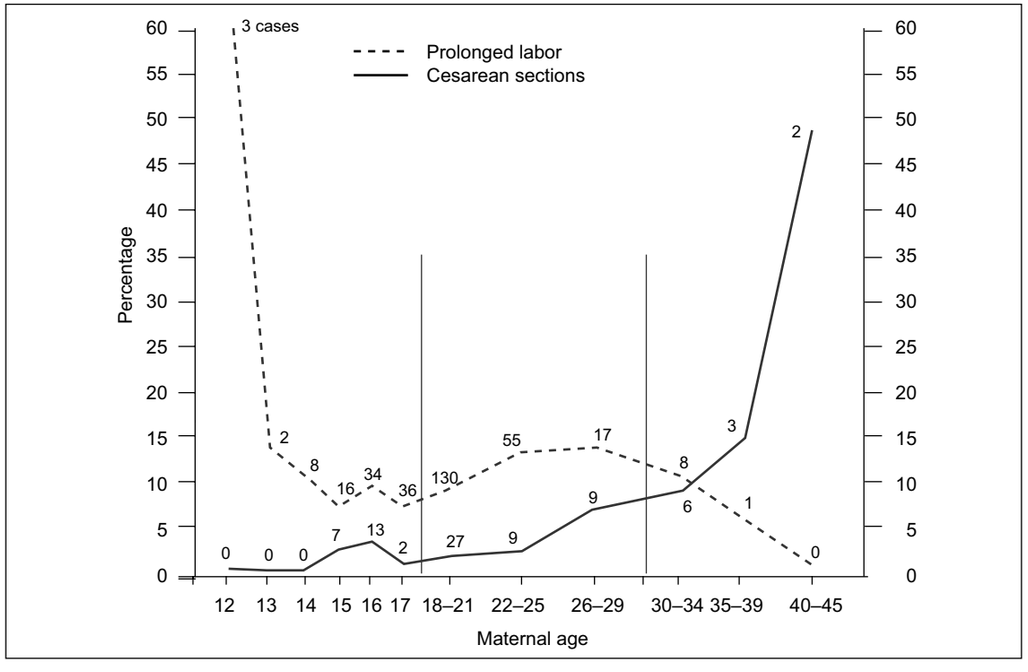

Figure 11 Maternal age, duration of labor and cesarean section rates. (Reproduced from Dodge *et al.*[47], with permission from Southern Medical Association)

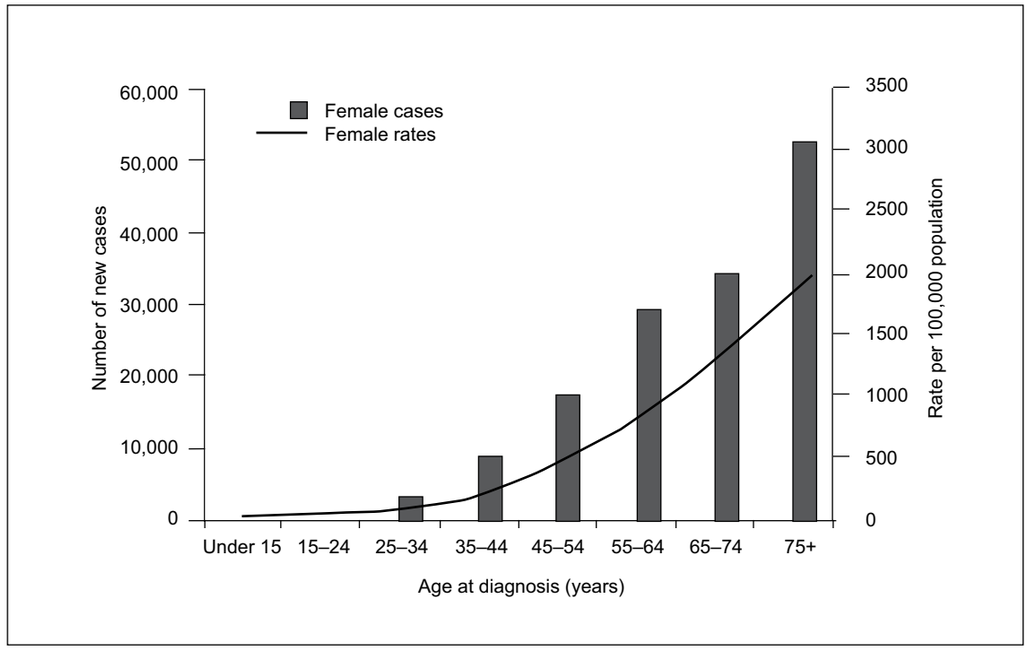

Figure 12 Number of new female cases and rates, by age, of all malignant neoplasms. (Office for National Statistics, UK, 2006[48])

include carcinoma of breast, lymphoma, carcinoma of cervix and ovarian tumors.

Maternal mortality and advanced maternal age

Modern day management of pregnant women who are older requires an understanding of the risks involved that result from the complex interplay between age, existing medical history and antenatal as well as perinatal complications. Maternal mortality is closely associated with maternal age. As shown in Figure 13, the highest mortality rates are among the oldest women as was evident in the Confidential Enquiry into Maternal and Child Health enquiries of 2003–2005, UK, in which the linear trend by age was statistically significant[22]. Stated another way, the average maternal mortality rate (MMR) increases as a function of age[38], and this increased risk is operational regardless of parity, time of entry into prenatal care and level of education.

Co-morbidities are also much more prevalent in older age, including cardiovascular disease, hypertension and multiparity, all of which directly contribute to the increase in MMR seen in older age[49]. These conditions also result in recognized complications of pregnancy, such as pregnancy induced hypertension, abnormal fetal growth, placental abruption and an increased rate of cesarean deliveries[49]. The risk of death from complications such as pregnancy induced hypertension, infection, embolism, hemorrhage and cerebrovascular disease is more than doubled in women over 30 compared to those who are younger[50]. In addition, psychiatric causes of death, such as postnatal depression, are more prevalent in women of older age.

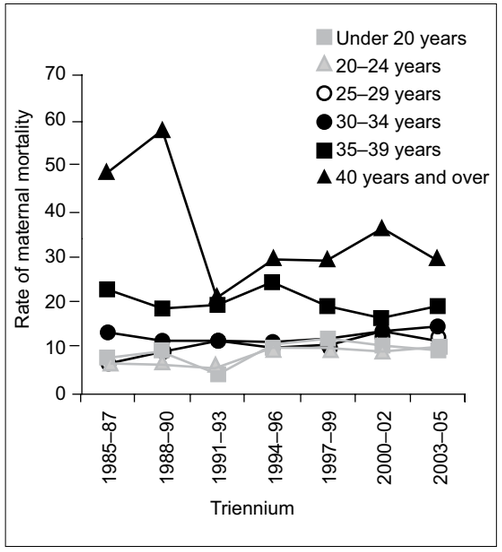

Figure 13 Maternal mortality and maternal age[22]

ETHICAL ISSUES AND OLDER PARENTS

Older age motherhood is generally associated with a greater level of educational achievement[51], and a large number of women presently elect to pursue educational programs and careers in fields that were conventionally occupied by men. In spite of this, it is not clear whether better educated women are delaying childbearing in order to reach a point of professional and financial security, or whether the pursuit of a better career leads to an unwanted but inevitable postponement of childbirth. With divorce figures on the rise, it is much more common for women to wed again in midlife, and then desire to have another child. Despite this growing trend, it will probably be another 15 years before information about both parents and children from the perimenopausal pregnancies becomes available to assess problems associated with facing retirement and adolescence at the same time.

When children face bereavement and orphanhood at a young age, emotional consequences may be devastating and potentially disabling. Even when the child does not have to face parental loss, the social stigma of being taken to and picked up from school by an uncharacteristically older parent may burden the child with psychological sequelae and prevent him/her from achieving an essentially normal childhood. Moreover, the inevitability of reduced stamina and energy which often accompanies older age may have a negative impact on the welfare of the offspring, as the older parent struggles to meet the demands of a growing child in its development.

Whilst a lot of women will already be aware of the significance of these potential problems, many still choose to attempt pregnancy at any cost, be it monetary, physical or psychological, despite the presence of significant co-morbidities. For some, the drive to have children is so strong that they willingly risk their livelihoods and even ultimately their own lives for the sake of bringing a child into the world and thus being a biological mother. This desire is undeniable and long has been defined as the very essence and meaning of womanhood.

Setting aside the emotional desire to have children, several objective reasons support childbearing at a later age and actually are of potential benefit in contrast to being a disadvantage. First, the financial security that an older parent has is undeniable. Second, an older parent typically experiences less pressure in the professional environment, being able to spend more time parenting, something that younger couples often find difficult and which accounts for the increasingly common circumstance in which young children are raised by their grandparents. Last, but hardly least, older parents often are better equipped with the emotional maturity required to raise a child and deal with the hurdles that child-rearing presents.

Age related attributes, often characterized merely as life experience and wisdom, may also mean that older mothers are more confident about their child-rearing skills and ability

to handle problems. In women who entered oocyte donation and IVF programs at later ages, there is evidence of a better relationship with their child and a greater degree of emotional involvement when the child is very young[52], as well as a considerably lower level of parenting stress[53]. Once the child reaches the age of 2, there appear to be no overt differences in parenting behavior compared to couples that conceived naturally[54].

CONCLUSION

In this age when women in Western societies seem to be able to have it all, there lies the untold truth about the private grief of older women, who for a number of reasons within and outside their control, have found themselves facing the prospect of childbearing in older age. The social and financial gains that come with women's new-found freedoms are tempered by the unrelenting biological decline of their fertility with advancing years, and this has forced many women into 'biopanic'.

As obstetricians and gynecologists, we have a duty to address the growing epidemic of aging motherhood and the complications that arise from this, as well as to inform women of the risks associated with delayed childbearing. Part of this duty includes trying to mount national and international efforts to facilitate childbearing with the option of career breaks, an ability to return to full- or part-time work after childbirth, and provision of adequate childcare and flexibility of working hours, among other possibilities.

Having said this, women should not be made to feel anxious or forced into childbearing when they may not feel prepared. They should not have to make a choice (however informed or ill-informed it may be) between having a career and reproducing within a safe biological window. For those women who desire to have children at an earlier age, they should not have to bear any adverse consequence from this decision, such as a diminution of their life plans and choices, nor should they be stigmatized for their decision or penalized in their professional spheres.

Society has a responsibility to make adequate provisions so that childbearing remains a free choice for women. Medicine, too, needs to realize that the persisting trend in older age motherhood is unlikely to be reversed and, should therefore, continue its present research into new methods of assisted reproduction, such as cryopreservation, to develop reliable means of reproduction for those women unable to conceive naturally, for those undergoing oophorectomy or chemotherapy for neoplastic disease, and for those wishing to conceive in older age for reasons both within and outside their influence.

Some women will inevitably fall outside of this range, for a number of personal and social reasons, and it will be up to us, as obstetricians and gynecologists to advise, as honestly and openly as possible, on the risks involved.

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2
Preconceptional counseling

Rahat Khan and Hassan Shehata

INTRODUCTION

Preconceptional counseling is different from antenatal care and should not be confused with it. In particular, it is more important than antenatal care, as 30% of pregnant women begin traditional antenatal care in the second trimester and after the period of maximal organogenesis (between 3 and 10 weeks' gestation)[1]. *Preconception care refers to interventions that aim to identify and modify biomedical, behavioral and social risks to women's health or pregnancy outcome through prevention and management*.

To date, the evidence as to the best means for delivering preconception care is limited. The Preconception Care Work Group of the Centers for Disease Control USA recommends that preconception care should be an essential part of primary and preventive care, which involves good communication and liaison between the primary and secondary care providers[2–4].

Preconceptional evaluation and counseling:

- Begin with attitudes and practices that value pregnant women, children and families, and respect the diversity of people's lives and experiences
- Incorporate informed choice, thus encouraging women and men to understand health issues that may affect conception and pregnancy
- Encourage women and their partners to prepare actively for pregnancy, enabling them to be as healthy as possible
- Attempt to identify the risks of pregnancy for the mother and her fetus, educate about these risks, and institute proper interventions including referral to specialists before conception.

Depending on their personal choice, women can go to any of the following health care providers for preconceptional counseling:

- Local doctor (general practitioner or family physician)
- Private obstetricians and gynecologists, specialists and obstetric physicians.
- Maternity hospital clinic, preconception health clinics or organizations
- Family planning, community health center or women's health nurse.

Health care providers can dispense preconceptional care and counseling during any encounter involving contraception, infertility, pregnancy testing, evaluation for sexually transmitted disease or vaginal infection, or periodic health examination, especially if the woman has pre-existing medical problems.

FACTORS ADVERSELY INFLUENCING PRECONCEPTION CARE

- *Unplanned pregnancy* In one US study, 40% of the mothers surveyed within 3–6 months after delivery reported that their pregnancy was unplanned; of these,

two-thirds had one or more indications for preconceptional counseling (smoking and drinking within 3 months of pregnancy, low body mass index (BMI) or late booking)[5].

- *Financial issues* A number of women with low income may have difficulties with child care and transportation, or may be reluctant to seek pre-pregnancy counseling. In the USA, on the other hand, preconceptional counseling often is not fully reimbursed by third-party payers. It is for this reason that it was proposed that it be included in a variety of otherwise routine encounters (see above).
- *Inadequate training of health care providers* All women's health care providers should be trained to provide adequate assessment of risk factors in pregnancy and offer appropriate recommendations for interventions.
- *Lack of co-ordination between primary and secondary care providers* As lack of co-ordination can represent an important barrier to optimum pre-pregnancy care, health care systems should develop policies for timely referrals to specialists and timely appointments.
- *Risk factors for adverse outcome* These include advancing maternal age, genetic history, infertility, fetal aneuploidy, gestational diabetes, pre-eclampsia and prior stillbirth, among others.
- *Lack of knowledge and education about health and pregnancy* Basic patient education should be an integral part of all women's health care provider systems, as numerous women have multiple risk factors and are unaware of the adverse pregnancy outcome associated with them.

COMPONENTS OF PRECONCEPTIONAL COUNSELING

The three integral components of pre-pregnancy counseling are:

- Identification of risk factors related to pregnancy
- Patient education regarding pregnancy risks, management options and reproductive alternatives
- Initiation of interventions, when possible, to provide optimum pregnancy outcome.

Risk identification

Thorough history taking is the key to risk assessment in any woman planning a pregnancy. This can be accomplished at the primary or specialist care level after referral.

Physical examination

A preconceptional health check does not necessarily involve a 'hands-on' physical check; rather, it focuses on obtaining information and discussing health issues to help the woman and her partner make informed decisions. A routine periodic health examination is all that is needed, documenting maternal BMI, assessment of breasts, thyroid, heart, skin, cervical smear and, if indicated, screening for *Chlamydia* and gonorrhea. As dental caries and other oral diseases are common and may be associated with preterm delivery, inspection of the oral cavity should be included in any examination protocol, thus, prompting referral to a dentist when appropriate.

Laboratory assessment and screening

The choice of laboratory tests depends upon the general guidelines recommended for all pregnant women and the individual's personal medical history.

Routine laboratory testing includes:

- Rubella and varicella titer, the latter being particularly important in women with a negative history of varicella
- Screening for hepatitis B, syphilis and HIV in all antenatal pregnant women
- Complete blood count with red cell indices (mean corpuscular volume (MCV) less than 80 may indicate hemoglobinopathy).

Interventions

Preconceptional interventions are directed at educating the patient, providing optimum therapy for medical disorders and, when appropriate, referral for specialized care.

Age-related risk

Women should be clearly informed that advanced maternal age is associated with an increased risk of conditions such as infertility, fetal aneuploidy, stillbirth, gestational diabetes and pre-eclampsia, among others.

The risk of fetal chromosomal anomalies, in particular Down's syndrome, increases sharply with increasing maternal age. The estimated risk of having a baby with trisomy 21, 18 and 13 is 6 per 1000 live births at age 35 years, 15 at age 40 years and 54 at age 45 years. There is also an increased risk of miscarriage, twins, fibroids, hypertension, gestational diabetes, labor problems and perinatal mortality, although it is equally true that most pregnancies in older women who do not have underlying diseases are uneventful.

Couples should be told that the probability of conception is highly dependent on maternal and, to a lesser extent, paternal age and they should take this into account in family and career planning.

Medical conditions

Data from clinical trials demonstrating improved outcome with preconceptional intervention exists for many chronic conditions, including diabetes mellitus, autoimmune conditions, hypertension, renal disease, thyroid disease and cardiac problems[6,10–12]. It is important to clarify the following points in history on the record:

- All medical and surgical conditions for which a woman has been treated, as it is useful for discussing the effect of pregnancy on these conditions and the effect of such disorders on pregnancy
- Contact details for present and past specialist care providers.

Pre-existing diabetes mellitus (see Chapters 5 and 32)

- For women with pre-existing diabetes, pre-pregnancy tight glycemic control is associated with enhanced pregnancy outcome; pre-pregnancy counseling provides an opportunity for assessment of diabetic retinopathy, nephropathy and neuropathy. Poor control of diabetes increases the risk of major fetal congenital abnormalities and miscarriage[6].
- Referral should be made to a specialist who cares for patients with diabetes (if contact has not been previously established) and, if available, to a diabetic preconceptional counseling clinic.
- The safety of oral hypoglycemic agents is now well established, and patients should be informed that outcomes are improved in women taking oral agents and comparable to those of insulin.
- Women should receive preconceptional folic acid (5 mg/day) up to 3 months into pregnancy as well as in the months preceding conception[26,27].

Chronic hypertension (see Chapter 12)

- The goal should be to control blood pressure prior to conception for any woman on angiotensin converting enzyme (ACE) inhibitors; the health care practioner should be satisfied with control, and effective contraception is advisable.
- All women with hypertension should be referred to a specialist for advice on drug manipulation and to organize shared care monitoring.
- ACE inhibitors should be avoided during pregnancy (fetal growth restriction, oligohydramnios, renal failure in fetus). Methyldopa or labetalol are the drugs of choice in pregnancy.

Asthma (see Chapter 4)

- Patients should be advised to use their peak flow meters regularly.
- Women with repeated asthmatic attacks or severe disease should be referred to a specialist in asthma therapy and not managed by the local doctor.
- If necessary, the use of steroids (inhaled and systemic) in pregnancy is generally safe.

Thyroid disease (see Chapter 6)

- Severe and untreated thyrotoxicosis should prompt referral to an endocrinologist during the preconceptional period, as this condition can lead to anovulation, miscarriage, growth restriction and preterm delivery[7]. Patients with elevated thyroid stimulating antibodies who become pregnant have the risk of neonatal/fetal thyrotoxicosis.
- There is insufficient evidence to recommend for or against routine screening of thyroid function and antibodies in women planning a pregnancy[8].
- In known hypothyroidism, thyroid function tests (TFTs) permit evaluation of adequacy of treatment and, if needed, support referral to specialist care.
- In newly diagnosed hypothyroidism, specialist advice should be sought about the levothyroxine starting dose and the woman should be referred for specialist management.

Cardiac problems (see Chapter 3)

- Women with a history of cardiac problems should be referred to a cardiologist for baseline cardiac assessments and discussion of potential pregnancy risks.
- Adequate diagnosis and functional assessment of the severity are necessary to predict maternal and fetal risks.
- Women advised against pregnancy should be given appropriate contraception.

Epilepsy (see Chapter 11)

- Women should be referred to a neurologist for a thorough discussion of the risk of anticonvulsant medications, adjustment of drug regimen and close monitoring during pregnancy.
- Polytherapy should be avoided to minimize the teratogenic effects of anticonvulsants.
- Preconceptional folic acid (5 mg/day) is advised for women on anticonvulsants[28,29].
- Prescription of an oral contraceptive pill with 50 μg of ethinylestradiol should be considered.

Chronic renal disease (see Chapter 8)

- Blood pressure and baseline renal function tests should be performed; any woman with renal disease planning a pregnancy should be referred to a specialist.

- Women should be informed that the outcome of pregnancy and any adverse effects on underlying renal disease are influenced by the presence and degree of renal impairment, hypertension (10% risk of fetal loss if pre-existing) and proteinuria.
- Renal disease during pregnancy is associated with risk of prematurity, growth restriction and deterioration in maternal renal function.
- Women with renal transplants should be asked to avoid pregnancy for a minimum of 2 years until renal function is optimized on a reduced amount of immunosuppressants.

Autoimmune disorders (see Chapter 7)

- Most autoimmune conditions improve in pregnancy, except systemic lupus erythematosus.
- Referral should be made to an obstetric physician, as preconceptional counseling involves knowledge of anti-Ro/La, lupus anticoagulant, renal and blood pressure status.
- Maternal medications may need to be changed because of potential risks to the fetus.
- Pregnancy outcome is improved if pregnancy occurs in remission period; the increased risks of pre-eclampsia, miscarriage, fetal death and growth restriction are related to the presence of anticardiolipin antibodies or lupus anticoagulant, lupus nephritis and hypertension.

Venous thromboembolism (see Chapter 9)

- Specialist advice should be sought for women who have a past history of deep venous thrombosis (DVT) or pulmonary embolism (PE), or with an abnormal thrombophilia screen.
- Women on warfarin planning a pregnancy should be referred to a specialist for advice. Warfarin is teratogenic and stopping or switching over to low molecular weight heparin, before the 6th week of pregnancy may minimize this risk.
- Inherited or acquired thrombophilia may also be responsible for recurrent fetal loss, pre-eclampsia and fetal growth retardation.

Hemoglobinopathies

- All women with sickle cell syndrome or thalassemias should be referred to a specialist/hematologist. Partners should be screened appropriately and advice sought if the trait is identified.
- Hemoglobin electrophoresis detects beta thalassemias, but alpha thalassemias can only be confirmed by globin chain synthesis. Ethnic minorities should be screened for particular traits (Asians and Cypriots for beta thalassemia; Africans, Afro-Caribbeans, Afro-Americans and Asians for sickle cell).

Review of medications
(see Chapters 22 and 23)

It is important to minimize exposure to all non-essential drugs, including self-medication with over-the-counter drugs.

Dietary evaluation (see Chapter 22)

- Vegetarians are at risk of various nutritional deficiencies and may benefit from nutritionist referral.
- Asian women are at risk of vitamin D deficiency and may benefit from a specific supplement.

- Eating habits should be reviewed, and women should be asked to avoid cat and sheep litter; uncooked meat, fish and eggs; and unpasteurized milk and soft cheese because of dangers of toxoplasmosis and listeriosis.
- Undiagnosed or untreated celiac disease in both men and women may cause subfertility, which resolves after adoption of a gluten-free diet.
- Megavitamins, non-essential dietary supplements and herbal preparations should be discontinued, as their risk to the fetus has not been evaluated. Multivitamins containing more than 5000 IU of vitamin A should be avoided.
- Women with phenylketonuria are at a high risk of having a baby with mental retardation and should be placed on a special diet to reduce levels prior to conception.
- All women planning a pregnancy should be on 400 μg/day of folic acid at least 3 months prior to conception to reduce the incidence of neural tube defects, such as spina bifida, by 72%.

Body mass index (see Chapter 30)

- Approximately, 60% of American women are overweight and 33% are obese. Women who are underweight or overweight are at risk of subfertility and may need referral to a pre-pregnancy weight management clinic and dietician. Problems with obesity and low weight are not confined to the American population, and obesity is almost as prevalent in the UK and in parts of Europe. In the UK, the prevalence of obesity among women of reproductive age is expected to rise from 24.2% in 2005 to 28.3% in 2015[30].
- Maternal obesity (BMI more than 30 kg/m^2) is associated with infertility, reduced *in vitro* fertilization (IVF) success rates, miscarriage and several pregnancy complications, such as gestational diabetes, pre-eclampsia, stillbirth, congenital anomalies in the fetus and postpartum complications.
- The overall health benefits of achieving a normal BMI pre-pregnancy are well described. Obesity-related hormonal changes appear to adversely affect sperm parameters and can cause erectile dysfunction.
- Obese women should be referred to a weight management clinic and dietician; women with polycystic ovaries should be referred to a gynecologist.

Past obstetric and gynecological history

Past obstetric and gynecological history is important for identifying factors that may contribute to infertility or pregnancy complications in the future.

- History of irregular menstrual cycles, abnormal cervical smear, ectopic pregnancy, pelvic surgery or uterine fibroids (associated with miscarriage and preterm birth) should be sought.
- Past history of sexually transmitted diseases, including the date and types of treatment should be noted.
- Previous reproductive history should be taken including any recurrent miscarriages, stillbirths, low birth weight, preterm births, congenital anomalies, antenatal problems and the mode, place, complications of delivery and type of contraception.
- All women who have had three consecutive miscarriages should be referred to a gynecologist or recurrent miscarriage specialist for identification and management of any treatable cause (see Chapter 17 on recurrent miscarriages).
- The recurrence risk of an adverse outcome (e.g. miscarriage, intrauterine growth restriction, pre-eclampsia, congenital anomaly, perinatal death) should be discussed with women who have a history of these specific pregnancy complications.
- Genetic screening should be advised for couples who have had a previously abnormal fetus, three recurrent fetal losses or have a personal or family history of a genetic problem.

Family history (see Chapter 31)

- Enquiries should be made about family history of Tay Sachs disease (Ashkenazi Jews), sickle cell disease (Africans/Afro-Caribbeans, Afro-Americans, Asians), thalassemia (Mediterranean and Middle Eastern origins), cystic fibrosis, epilepsy, thrombophilia, hemophilia, congenital abnormalities, metabolic disorders and mental disorders.
- Certain ethnic minorities have a high prevalence of being heterozygous carriers of certain autosomal recessive disorders and both partners should be screened as this allows them to make informed decisions about having children.

Psychosocial problems

- It is important to screen for domestic violence, work-related issues, lack of support and financial issues that can be a barrier to preconception care[20].
- Women with mental health issues should be identified and actions taken to ensure they are under specialist care. Common conditions necessitating referral are depression, bipolar affective disorder and schizophrenia, and history of postnatal depression[21] (see Chapter 13).
- Women should be reassured that there is no indication to routinely stop tricyclic antidepressants or selective serotonin re-uptake inhibitors prior to or in early pregnancy.
- Women who are on mood stabilizing antiepileptic drugs should be on 5 mg/day of folic acid preconceptionally and during first 3 months of pregnancy[28,29]. This dose is higher than that universally recommended to other women.
- Lithium is highly teratogenic if taken in the first 12 weeks of pregnancy (risk of Ebstein's anomaly 4–12%) and should be given only if necessary by close monitoring of lithium levels. Schizophrenic women may be advised to continue maintenance therapy and discuss the relative risks/benefits of the selected agents.

Illicit drug use

- Cocaine use in pregnancy is associated with miscarriage, abruption, premature birth and low birth weight; opiate use is associated with growth restriction and preterm birth[14,17,19,25].
- All women addicted to heroin should be encouraged to enter a detoxification program.
- Intravenous drug abusers should be screened for hepatitis B, C and HIV, alcohol and tobacco use.
- A multidisciplinary approach is essential as is screening for sexually transmitted diseases.

Alcohol use

- It is important to elicit a detailed history of alcohol consumption in terms of amounts, duration and the propensity to binge drinking. Causes of subfertility in these women include reduced ovulation and endometriosis.
- Maternal consumption of 15 units/week is associated with a reduction in birth weight and in excess of 20 units/week is associated with intellectual impairment in the child.
- High levels of alcohol consumption during pregnancy result in the fetal alcohol syndrome (FAS), which includes growth retardation, mental retardation, facial anomalies and behavioral problems[9,13,15,16,18]. It is seen in 33% of babies born to mothers who drink 18 units/day. There is no clear safe level of consumption. All women should be advised to reduce their alcohol intake if they are planning a pregnancy, although it has been posited that one or two drinks, once or twice a week, is unlikely to harm the fetus[9].
- It is important to identify women who drink heavily and are likely to continue drinking throughout pregnancy so that appropriate help and support can be offered.

Smoking

- Approximately, 23% of women smoke in pregnancy, and they should be informed of the risks associated with smoking, which include miscarriage, stillbirth, growth restriction, preterm delivery and sudden infant death syndrome[9,13,19].
- All women who smoke should be counseled on the benefits of smoking cessation and offered resources to help them quit smoking. Women who quit before pregnancy are less likely to relapse. Data on the use and relative risks of nicotine replacement therapy (NRT) in pregnancy are lacking.
- Bupropion should not be prescribed in pregnancy because of the lack of data on its safety in pregnancy.

Caffeine

- According to many publications, caffeine is the most widely consumed substance of abuse worldwide. The safe limit in pregnancy is thought to be 300 mg/day, which is equivalent to three cups of brewed coffee. Caffeine is present in chocolate, cola and energy drinks as well as in coffee and tea. Approximately 20% of American adults consume more than 300 mg of caffeine per day. Caffeine consumption of more than 250 mg/day is associated with a modest, but statistically significant decrease in fertility [9,19,22].

Exercise

- Women who exercise regularly should be advised to continue such activity. On the other hand, those who are inactive should start a gentle exercise program. Inadequate levels of exercise associated with obesity may be a more common cause of anovulation than exercise associated anovulation.
- In some epidemiological studies, more than 7 h/week of aerobic exercise is associated with ovulatory infertility and could be related to reduced progesterone levels and changes in the gonadotropin releasing hormone (GnRH), luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion[9]. Initiation of strenuous exercise in pregnancy should be avoided, including hot tubs and saunas.

Immunizations and infections

- Women of childbearing age should be asked for a history of any illness or immunizations.
- Non-pregnant women of childbearing age should receive all clinically indicated immunizations, preferably 1 month prior to conception.
- Having a clearly documented immunity to rubella is important, as primary rubella infection in the first 8–10 weeks of pregnancy can result in mental handicap, cataract, deafness, cardiac abnormalities and growth restriction in the fetus.
- Varicella infection in the mother during first 20 weeks of pregnancy can cause congenital varicella syndrome in the fetus. Varicella vaccine must not be given to pregnant women.
- Pregnant women are at increased risk of influenza infection complications. It is recommended that women who become pregnant during the influenza season receive the influenza vaccine, regardless of the stage of pregnancy. Pregnant women are also being encouraged to have swine flu vaccine.
- Patients at risk for hepatitis B infection (women with multiple sexual partners, parenteral drug users, household contacts, health care workers) should be offered hepatitis B vaccine.
- Women of childbearing age who are HIV positive should be offered preconceptional counseling with a HIV specialist.

Occupational and environmental exposure

- Questions about the woman's work, hobbies, pets and home environment can identify potential toxic exposures, such as working with organic solvents, X-rays, radioactive substances, toxoplasmosis (from changing cat litter boxes) and using lead paint or solder used for decorating[22–24].
- Risks from potential hazards at home (e.g. pets), at work and from farm animals should be assessed.
- Any woman who thinks that her occupation may pose a risk to pregnancy should be advised to discuss this with her employer or occupational health department, if possible, before getting pregnant.

SUMMARY AND RECOMMENDATIONS

- All women of childbearing age should be offered preconceptional counseling and evaluation.
- The goals of preconceptional counseling are to identify risks to the woman and her pregnancy, educate the patient and initiate appropriate interventions.
- Good communication between primary and secondary care providers is vital to optimize a woman's health prior to conception and ensuring timely referral.
- A thorough history will help in identifying risk factors to the woman and her pregnancy.
- A pregnant woman with a BMI of greater 30 kg/m^2 should be referred to dietician and specialist clinic.
- Women who are planning a pregnancy should be on folic acid 400 μg/day. Women who are diabetic or on antiepileptic medications should be on 5 mg of folic acid/day[26–29].
- An up-to-date cervical smear should have been taken.

- All women should be screened for hepatitis B, HIV, syphilis, rubella and varicella immunity.
- All medications should be reviewed and advice given on the use of over-the-counter medications.
- If applicable, advice should be given on stopping smoking, reducing alcohol intake, healthy eating and stopping illicit drug use. Psychosocial and domestic issues should be identified.
- Ethnic minorities should be screened for hemoglobinopathies and carrier state.
- Family history should be reviewed with referral for genetic counseling, if appropriate.
- Women with a history of recurrent miscarriages, stillbirth, pre-eclampsia or a previous small baby should be referred to an obstetrician/gynecologist or a specialist center for further investigations and discussion of recurrence risks.
- Women with chronic medical conditions should receive multidisciplinary care. Women with diabetes, chronic hypertension, renal or cardiac disease, thyroid problems, epilepsy or asthma should be advised to use effective contraception until seen by a specialist and plans for care have been discussed and put into practice.
- Women with mental health issues should be referred to a psychiatrist.
- Genetic counseling should be offered to all women with a previous abnormal fetus, personal or family history of genetic problems or a history of three recurrent miscarriages.
- A good occupational and environmental history should be sought to review all potential health and pregnancy hazards.

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Preconceptional evaluation of women with heart disease

Marla A. Mendelson

INTRODUCTION

Women reaching childbearing age may present with congenital or acquired cardiac disease. Cardiac complications arising during pregnancy impact morbidity and mortality of mothers and their unborn children. Anticipating cardiac problems in light of the expected hemodynamic changes of pregnancy is the basis of the preconceptional evaluation. Risks specific to each woman's particular disorder should be identified prior to conception, and intervention(s) may be required to improve cardiac status prior to pregnancy. For some women, pregnancy may worsen their cardiac condition and functional capacity, thus impacting their ability to gestate and, at a later date, to parent.

The normal hemodynamic changes of pregnancy pose potential problems for many women with pre-existing heart disease. Although the medical literature is replete with studies and case series of women who have successfully completed pregnancies despite having cardiovascular disease, it is important to anticipate those problems that may arise specific to the underlying heart disease[1–8]. The automatic dismissal of the possibility for successful pregnancy in a woman with underlying heart disease is inappropriate, although women with certain types of heart disease may not be able to sustain pregnancy without grave risk.

Overall, the objective is to provide a rational plan to encourage a pregnancy that is safe for both the mother and her developing fetus, to identify potential complications that may occur during pregnancy, and to review medications that may require change in anticipation of pregnancy. As most cardiac diseases have been reported during pregnancy, certain guiding principles have emerged for preconceptional evaluation and the potential complications that could arise during a pregnancy. Foremost, women with pre-existing heart disease require full evaluation prior to conception. Second, not only should the risk to the mother be identified but also potential risks to the developing fetus need be clarified and understood. For example, cyanotic heart disease has been associated with fetal prematurity, dysmaturity or low birth weight. Third, it is axiomatic that a woman with congenital heart disease may transmit this condition to her offspring. Finally, it is important to identify interventions that may improve the prognosis for any outcome of the pregnancy.

Recent literature has focused on outcomes in women with pre-existing heart disease and proposed and validated a risk scoring system[1,3,6,7,9,10]. Depending upon the country, the type of pre-existing cardiac disease in women of childbearing age may differ. For example, 55% of Brazilian patients had pre-existing rheumatic heart disease, whereas only 19% exhibited a congenital heart condition[6]. Distribution is different in studies based in the United States and Canada wherein 74% of

women had underlying congenital heart disease, 22% acquired heart disease and 4% isolated arrhythmias.

The adverse cardiac events common to all the studies include congestive heart failure, pulmonary edema, arrhythmias, thromboembolic events, angina, endocarditis and a decrease in the New York Heart Association functional class. Canadian researchers developed a risk score of one for each identified predictor of risk which includes: (1) prior cardiac event (heart failure, transient ischemic attack or stroke); (2) New York Heart Association class greater than two or the presence of cyanosis; (3) left heart obstruction with mitral valve area less than 2 cm^2, or aortic valve area less than 1.5 cm^2, or left ventricular gradient greater than 30 mmHg; and (4) ejection fraction less than 40%. In the population of women with congenital heart disease: zero risk points was associated with a 5% risk of adverse events; one risk predictor carried an 18% risk of adverse events; and two or more risk factors predicted a complication rate of 57%[10]. Predictors for neonatal complications included poor functional class of the mother or cyanosis, left heart obstruction, anticoagulation or multiple gestation.

HEMODYNAMIC RISKS OF PREGNANCY IN WOMEN WITH CARDIAC DISEASE

The overriding concern regarding maternal morbidity and mortality relates to the type of underlying heart disease and the degree of functional limitation. Women with pulmonary hypertension or systemic ventricular dysfunction cannot tolerate the hemodynamic changes of pregnancy; therefore, these problems constitute contraindications to pregnancy. Contraindications to pregnancy are listed in Table 1.

The expected hemodynamic changes of pregnancy vary with respect to the type of cardiac lesion. For example, the woman with mitral regurgitation, because of the vasodilatation and decrease in afterload occurring during pregnancy, may actually have a decrease in her valve regurgitation during pregnancy. The hemodynamic changes in pregnancy are summarized in Table 2. Simply put, the changes of pregnancy may be deleterious and not tolerated in the setting of impaired systemic ventricular function[5,9]. During pregnancy with its associated 50% increase in blood volume, the heart may become dilated, and this may lead to further dysfunction in an already compromised ventricle. Because these changes may

Table 1 Cardiac contraindications to pregnancy

Contraindication	*Potential risk*
Absolute: cardiac condition imperils maternal and fetal outcome	Worsening of function
Systemic ventricular dysfunction (New York Heart Association functional class III, IV)	Congestive heart failure; postpartum impairment
Pulmonary hypertension/Eisenmenger's syndrome	Increased maternal mortality; cyanosis; fetal loss
Relative contraindication: high-risk pregnancy anticipated	
Severe mitral or aortic valve stenosis	Congestive heart failure; atrial fibrillation; thromboembolism
Aortic dilatation (Marfan syndrome/ bicuspid aortic valve)	Aortic dissection or rupture
Prosthetic (mechanical) heart valve	Valve thrombosis or bleeding

Table 2 Summary of expected hemodynamic changes of pregnancy

Hemodynamic alteration	*Time of peak effect*	*Potential risks*
Cardiac output ↑30–50%	20–24 weeks	Women with limited cardiac function or reserve may develop congestive heart failure
Stroke volume ↑20%	20–24 weeks	Increased preload is a problem for obstructive lesions (mitral or aortic stenosis) or ventricular dysfunction
Heart rate ↑10–20%	Third trimester	Tachycardia causes palpitations and impairs ventricular filling
Blood volume ↑40%	20–24 weeks	'Physiologic' anemia of pregnancy caused by reduced increase in erythrocyte mass
Peripheral vasodilatation	Throughout	↓Blood pressure; ↓valvular regurgitation
↑Minute ventilation	Second trimester	Sensation of tachypnea or dyspnea

persist during the postpartum period as well, it is important that the preconceptional evaluation should attempt to anticipate whether further cardiac decompensation may occur as a result of the pregnancy.

Pulmonary hypertension constitutes a contraindication to pregnancy (Table 1). This may occur as primary pulmonary hypertension, which commonly occurs in young women; certainly any symptoms of exertional chest pain or syncope may be a manifestation of pulmonary hypertension. Pulmonary artery pressure may be estimated using non-invasive echocardiography testing. If concern is present about elevated pulmonary pressure, the patient may need to proceed to cardiac catheterization to assess the intracardiac and intravascular pressures, as pulmonary hypertension has been associated with 50% maternal mortality. Even secondary pulmonary hypertension due to the underlying congenital heart disease confers a risk of mortality. A woman having undergone surgical repair may have residual hypertension that could confer a pregnancy risk. Such risks persist into the postpartum period as well[5].

MATERNAL MEDICATIONS

It may not be prudent to abruptly stop all previously prescribed medications once it is known that a woman with a diagnosed cardiac condition is pregnant[11,12]. Medication choices are an important aspect of preconceptional counseling. Alterations in medications should be part of the preconceptional evaluation; normally this process involves changing the patient to medications that may be better tolerated and safer during pregnancy. Indeed, medications to improve cardiac status may be necessary for a successful pregnancy outcome. Certain of these have been classified as contraindicated during pregnancy and have received a Food and Drug Administration (FDA) classification of 'X'. The common cardiac medications and their potential problems for pregnancy are summarized in Table 3.

Unfortunately, research on medication during pregnancy is limited; even the FDA classification is based on isolated case reports and animal studies. Medication risks must always be outweighed by their potential benefits, and,

Table 3 Cardiac medication during pregnancy

Medication	*FDA class*	*Risks in pregnancy*	*Recommendations*
Warfarin	X	Teratogenic; bleeding	Avoid in first trimester and prior to delivery; dose <5 mg
Aspirin	C/D	Bleeding; early ductal closure	Low dose if possible
Digoxin	C		Continue
Diuretics	B/C/D	Hypovolemia; electrolyte disorder	Use only for congestive heart failure or pulmonary edema
Atenolol	D	Hypotension	Change to metoprolol
Metoprolol	C	Hypotension	Continue if indicated
Calcium channel blockers	C	Hypertension; uterine effects	Continue if indicated
Hydralazine	C	Hypotension; fetal thrombocytopenia	May be continued if necessary
ACE inhibitors	D	Fetal abnormalities	Discontinue; change to hydralazine
Amiodarone	D	Fetal thyroid disorder	Continue if necessary

ACE, angiotensin converting enzyme

in some populations as discussed below, women definitely need to continue to take their medications.

CONGENITAL HEART DISEASE

The population of women of childbearing age who were born with heart disease is increasing because of the advances in cardiac surgery, diagnosis and intervention during childhood. Each type of problem, whether it be a shunt, valvular or complex congenital heart lesion, needs to be examined uniquely with regard to potential risks of pregnancy.

Shunt lesions

Atrial septal defect

In an adult an unrepaired atrial septal defect (ASD) carries a theoretic risk of paradoxical embolus. This is of particular concern during pregnancy, because as the pregnancy progresses a woman becomes more hypercoaguable. Although earlier literature suggested such individuals be prophylacticly anticoagulated, this is not warranted in an ambulatory patient. The potential risk of arrhythmia, particularly supraventricular arrhythmia, is also present. If the defect is particularly large, bidirectional shunting may be present. In the setting of chronic right to left shunting, increases in the pulmonary pressure may result in Eisenmenger's syndrome, which results from progressive increases in pulmonary vascular flow causing changes within the pulmonary vasculature. The shunt eventually reverses from right to left, and the patient becomes cyanotic. In this setting, pregnancy is contraindicated because the patient cannot tolerate the hemodynamic changes of pregnancy. Also, cyanotic mothers have a high risk of having small for gestational age infants, which increases their risks. Echocardiography with Doppler may quantify the pulmonary artery pressure. If there is a concern regarding hypertension, a right-heart catheterization may be indicated for a definitive diagnosis. The overall

risk to the offspring is estimated at 8–10% if a maternal ASD is present[13]. Closure of the septal defect prior to conception may improve outcome, although it is best to wait 6 months after surgery or device placement for endothelization of the interatrial septum to occur before pregnancy is attempted.

Women with a repaired ASD may exhibit residual shunting which then would confer the risk of paradoxical embolus. The repair may consist of a surgically placed patch or catheter-based device, and the risk of arrhythmias may persist. Symptoms suggestive of arrhythmias should be investigated prior to pregnancy. Women born with a primum ASD may have also had a cleft mitral valve. Despite repair of the mitral valve in childhood, significant mitral regurgitation may be present in the adult. Although unrepaired, there is still an increased risk of congenital heart disease in the fetus. In one report women with shunt lesions had the highest prevalence of obstetric and cardiac complications[1].

Ventricular septal defect

An unrepaired ventricular septal defect (VSD) confers a risk of endocarditis, pulmonary hypertension and aortic valve insufficiency. Usually there is a high pressure left to right shunting, and endocarditis may occur. A high velocity left to right shunt over time increases pulmonary arterial flow causing permanent vascular changes within the lung and, subsequently, pulmonary artery pressure increase. This may also result in an Eisenmenger's syndrome (see above). Due to the severity of the shunt and proximity to the aortic valve of a membranous VSD, there may be progressive aortic insufficiency. Progressive aortic insufficiency, increasing pulmonary pressures or a history of endocarditis are indications to close a VSD. Echocardiography with Doppler should help identify complications of a VSD in the preconceptional evaluation. It is important to remember in a woman with the Eisenmenger's physiology syndrome that her risks persist after delivery when she is undergoing fluid shifts; they are also present with termination of pregnancy when there may also be fluid shifts and a drop in systemic pressure due to the effects of anesthesia. Such a decline in systemic pressure in a woman with Eisenmenger's physiology who already has a right to left shunt may worsen the right and left shunting thereby worsening the cyanosis.

After repair of a VSD, a residual shunt may put the patient at risk for endocarditis. A bundle branch block may be seen on the electrocardiogram, and, depending on the age of the repair, persistent elevation of pulmonary artery pressure may be noted by Doppler echocardiography or further defined by right heart catheterization.

Patent ductus arteriosus

An unrepaired patent ductus arteriosus (PDA) presents a theoretic risk of endarteritis and pulmonary hypertension. This risk is related to the persistence of the connection between the pulmonary artery and the aorta. In adult life the shunt would be from left to right, and, therefore, there would be increasing flow within the pulmonary vasculature. Theoretically there may also be associated Eisenmenger's physiology.

This lesion can be repaired during childhood when the PDA is ligated; pregnancy is well tolerated in patients who have had a repair. However, their offspring still carry a risk of congenital heart disease. The patient may also have had a closure using a coil in a catheter-based intervention; theoretically pregnancy should be tolerated well as long as there is no residual pulmonary hypertension.

Complex congenital heart disease

Coarctation of the aorta

The adult form of coarctation of the aorta represents a narrowing of the aorta distal to the

left subclavian artery. This condition often is diagnosed in childhood but may only present in adulthood. If this is the case, mild coarctation of the aorta is present, and patients develop an extensive network of collateral flow to supply their lower body. Associated bicuspid aortic valve with aortic valve pathology or progressive ascending aorta dilatation may also be present and dissection is possible at the site of coarctation[13].

A coarctation is either repaired or bypassed during childhood, or a stent may have been placed within the aorta. The women should be assessed prior to pregnancy because restenosis may have occurred. If so, stenting may be considered prior to pregnancy. After the stent is placed, pregnancy should be delayed approximately 6 months. Even in the absence of restenosis, the adult may experience persistent hypertension particularly with exercise. Medications for hypertension may need to be altered in anticipation of pregnancy, and the patient should be monitored closely for elevations in blood pressure and aortic root enlargement during pregnancy.

Tetralogy of Fallot

Women of childbearing age with an unrepaired tetralogy of Fallot are cyanotic and pregnancy is not advised. Most women of this age will have already undergone a repair and preconceptional evaluation to look for residual abnormal hemodynamics, pulmonary valve disease, ventricular dysfunction and arrhythmia or heart block[14,15]. Risk of sudden death is present in this population. Severe pulmonary insufficiency after repair has been associated with right ventricular enlargement or dysfunction during pregnancy[2,15]. There also may be a risk of sudden death if the QRS is particularly prolonged (over 160 m/s). The overall risk of fetal loss and congenital heart disease is increased, and other associated problems may be present, for example a 22q11 deletion, which is associated with the DiGeorge's syndrome. Such patients may have tetralogy of Fallot or interrupted aortic arch.

Ebstein's anomaly

Women with mild forms of the Ebstein's anomaly may not have required repair prior to reaching the childbearing years but should nonetheless undergo complete evaluation. Assessment should focus on the extent of tricuspid regurgitation, the presence of cyanosis and existence of residual right ventricular dysfunction. In Ebstein's anomaly the tricuspid valve is set low into the right ventricle, so that the right ventricle becomes atrialized. Severe forms are diagnosed during childhood and repaired. After repair it is important to assess the patient for residual hemodynamic abnormalities such as tricuspid insufficiency and residual cyanosis. The tricuspid insufficiency may increase and be accompanied by right ventricular failure during pregnancy. Heart block and arrhythmias also may occur. The association of Wolff-Parkinson-White syndrome (accessory bypass tract) confers the risk of atrial arrhythmias in these patients. Fetal risks have been described, including low birth weight and fetal loss, both of which seem to be associated with maternal cyanosis. The risk of congenital heart disease in the fetus has been estimated at 6%[13].

Single ventricle

Women born with a variant single ventricle variant may have undergone a variety of surgical interventions. Single ventricle variants include tricuspid artresia or double outlet right ventricle. Such individuals may have had a Glenn procedure, in which the superior vena cava flow is directed to the pulmonary artery, and a Fontan procedure, in which in the inferior vena cava flow is directed to the

pulmonary artery either outside the heart or incorporating some of the right atrium. Recent approaches have placed external conduits to the pulmonary artery, but variations of the Fontan repair are reported. All women who have had a Fontan procedure should have preconceptional evaluation[13]. There have been many case reports of successful pregnancies; however, there are multiple variations of the Fontan conduit[15–17]. Revision of the Fontan may be recommended prior to conception. Anticoagulation should be continued. Maternal risks include atrial arrhythmias and heart block. Women who have underlying ventricular dysfunction may not be able to sustain a pregnancy. They may exhibit edema and ascites if there is failure of the Fontan circuit, and both should be identified prior to pregnancy. Fetal risks include spontaneous abortion, premature birth and embryopathy, because these patients are often continued on warfarin, in addition to other medications[15–17].

D-transposition of the great vessels

In women born with d-transposition of the great vessels, the aorta arises from the right ventricle and the pulmonary artery from the left ventricle. These women will have undergone some type of repair prior to reaching childbearing age and require full evaluation including a clinical, functional and echocardiographic evaluation to look specifically for atrioventricular (AV) valve regurgitation, atrial arrhythmia and, importantly, systemic ventricular function[18]. After an atrial switch procedure (Mustard/Senning), the right ventricle serves as the systemic ventricle and over time may dilate in response to the volume load[19]. There may be an overall decrease in systemic ventricular ejection fraction. An atrial switch (Mustard/Senning procedure) diverts the incoming flow to the appropriate ventricles: the incoming deoxygenated vena caval flow is directed by a baffle to the mitral valve of the left ventricle and thence to the pulmonary artery. At the same time, the pulmonary arterial flow is directed by another baffle to the tricuspid valve, right ventricle and aorta. Women who have had the atrial switch procedure need to be assessed for right ventricular size and function. The right ventricle is a systemic ventricle and needs to sustain the increase volume load of pregnancy. The patient may have had a Rastelli procedure in which there is a left ventricle to aorta baffle with closure of the VSD. Such individuals need to be assessed for left and right ventricular obstruction; in addition their systemic ventricular function should be assessed, although they do have a left ventricle for their systemic flow. Pregnancies after atrial switch have been described[18,19]. Reported risks include systemic ventricular failure and arrhythmias. Obstetric complications include premature delivery, growth retardation and thromboembolic complications[19].

The more up-to-date repair is an arterial switch (Jatene procedure), in which the great vessels are actually switched and the coronary arteries reimplanted. Case reports of pregnancy after the arterial switch procedure are available. Because the coronary arteries are reimplanted, the arteries and the aorta need to be assessed. The same may be said for functional capacity prior to pregnancy.

L-transposition of the great vessels

L-transposition of the great vessels may not be diagnosed until adulthood due to the associated pulmonic stenosis, VSD or congenital heart block. The right ventricle is on the left side and connected to the aorta. Having to serve as the systemic ventricle, it may fail over time. Preconceptional evaluation should assess systemic ventricular function, and the extent of AV valvular regurgitation which may worsen as pregnancy progresses[20]. Echocardiography is essential to assess anatomy and AV valve function. A pacemaker may have been placed

and its status requires substantiation. Magnetic resonance imaging (MRI) may be useful to evaluate anatomy. With stress testing aerobic capacity is paramount, and pregnancy is not well tolerated if aerobic capacity is less than 75% of that predicted. In a study of 60 pregnancies in 22 women, there was a 16% miscarriage rate, but no congenital heart disease was identified in the offspring. The maternal risks included congestive heart failure which was related to systemic AV valve regurgitation[20].

Valvular lesions

Women of childbearing age may have been born with valve disease or acquired it after a bout of rheumatic fever[21]. Rheumatic heart disease is less common today in the United States and Europe, but remains a problem for women of childbearing age in the Philippines, India and the Middle East. Despite its etiology, valvular heart disease may be complicated by the expected hemodynamic changes of pregnancy with increased preload and decreased afterload[22]. Endocarditis may recur during pregnancy resulting in further valve deterioration. Most patients with valvular heart disease should undergo preconceptional evaluation which may include stress testing to detect dynamic changes in valve function after exercise.

The aortic valve

The woman born with a bicuspid aortic valve does not have significant hemodynamic changes within the valve or may have a combination of aortic stenosis and aortic insufficiency. When severe aortic stenosis is present, pregnancy should be discouraged if the aortic valve area is less than 1.0 cm^2. The concern is that the volume load of pregnancy may be difficult to tolerate and increase the incidence of congestive heart failure during pregnancy[23,24]. Pregnancy should be avoided and valve repair considered if the woman develops dyspnea, syncope or angina. It may be best to proceed with valvular repair in anticipation of pregnancy.

Aortic insufficiency

Aortic insufficiency is often well tolerated in the adult patient. It is important, however, to assess the degree of ventricular dilatation; if the ventricle is quite dilated and/or the patient is symptomatic, intervention prior to pregnancy is advisable. It is interesting to note that valve regurgitation may actually decrease during the course of a pregnancy, because of the natural afterload reduction that occurs. If ventricular function and dimensions are normal, on the other hand, pregnancy is usually well tolerated[22].

A bicuspid aortic valve, may be associated with the aortic enlargement which needs to be assessed prior to and during pregnancy. If enlargement is present, beta blockade may protect the aorta from enlargement as seen in the setting of Marfan syndrome. During pregnancy changes may occur within the media of the vessel wall that promote aortic enlargement[25]. Pregnancy should be discouraged in the woman with Marfan syndrome who has an aortic root dimension greater than 4 cm. If a woman with aortic dilatation becomes pregnant she should be maintained on beta blockers. The aortic root dimension should be monitored by echocardiography during the course of the pregnancy because of a theoretic risk of aortic enlargement. In addition, patients may not be able to tolerate the prolonged Valsalva maneuver which may occur during the pushing of the second stage of labor, as there may be strain on the aortic wall.

Supraventricular aortic stenosis

Supraventricular aortic stenosis is often associated with William's syndrome and may be identified if there is a family history of hypertension, coronary artery disease or stroke. Pregnancy should be discouraged if significant obstructive coronary involvement or aortic disease is present[13].

Pulmonic valve

The pulmonary valve is often involved in complex congenital heart disease. The patient may also present with isolated pulmonic valve stenosis or insufficiency. Pregnancy is usually well tolerated if pulmonic valve stenosis is mild to moderate. If severe, on the other hand, a valvotomy should be considered prior to pregnancy[22]. This catheter-based procedure relieves significant gradients across the valve and thereby makes the patient a better candidate for pregnancy. It must to be remembered, however, that even with right ventricular outflow obstruction the right ventricle is going to increase in volume during the pregnancy; this may not be well tolerated and theoretically could result in tricuspid regurgitation.

Pulmonic insufficiency

Pulmonic insufficiency is an isolated finding; it is often well tolerated but becomes more complicated if it appears following complex congenital heart surgery such as that for tetralogy of Fallot. The outcome of pregnancy may be determined by right ventricular size and function. Right ventricular function may be identified by stress testing to assess right ventricular reserve with exercise. With severe pulmonary insufficiency, the right ventricle is impaired either at rest and/or with exercise, so much so that there may be an indication to replace the valve with a homograft to permit a less potentially complicated pregnancy.

Mitral valve

Mitral valve stenosis is usually rheumatic in origin. The major risks of mitral stenosis include pulmonary edema, atrial thrombus and embolic atrial fibrillation. In the presence of atrial fibrillation, congestive heart failure may result with the loss of atrial 'kick'. This circumstance may be accentuated during pregnancy or if the patient is already volume overloaded. It is therefore important to identify mitral stenosis prior to pregnancy. As a woman with mitral stenosis develops atrial fibrillation or becomes hypercoaguable, she may develop thrombi in the left atrium and be at risk for thromboembolic complications[21,26]. This patient needs to be followed closely during pregnancy for changes in rhythm and/or fluid overload. Valve repair may be indicated prior to pregnancy. Percutaneous balloon valvotomy has been used during pregnancy when congestive heart failure develops. Prior valve replacement with a mechanical prosthesis creates potential problems with regard to anticoagulation. Several strategies are available for heparin and warfarin anticoagulation[27–30].

Mitral insufficiency

This problem is usually well tolerated during pregnancy; with the natural afterload that occurs with vasodilatation, it may actually decrease. Mitral insufficiency may be seen after ASD repair, because primum ASD may be associated with a cleft mitral valve. In view of the fact that a cleft mitral valve may have been repaired during childhood but, as an adult, residual mitral regurgitation may be present, it is important to look for this prior to pregnancy. If mitral regurgitation is severe, the patient may benefit from valve repair prior to pregnancy.

Tricuspid valve

Tricuspid stenosis is most often identified during childhood, and patients undergo repair (discussed below). Tricuspid valve insufficiency is often well tolerated during

pregnancy, although it may increase with the hemodynamic changes of increased volume.

AORTIC DISEASE

Marfan syndrome

Marfan syndrome is characterized by cardiac involvement, including progressive aortic dilatation and mitral valve regurgitation. In women with aortic dilatation, aortic dissection and rupture may occur in pregnancy, particularly if the aorta is 40 mm or greater in diameter[31–36]. Aortic dissection/rupture can occur at anytime during the third trimester when there also may be a worsening of mitral regurgitation. The autosomal dominance of Marfan syndrome itself presents a risk to the fetus. The patient needs to be followed during pregnancy with echocardiography to assess the valves and aortic root. Beta blockade should be continued, but only metoprolol is recommended during pregnancy (Table 3). Women on losartan should be changed to a beta blocker prior to conception.

ARRHYTHMIAS

Women of childbearing age may have a history of a prior arrhythmia[37,38]. This may occur in the absence of structural heart disease but is common in women with congenital heart disease[39]. Recurrence risks in pregnancy vary greatly depending on the arrhythmia. Recurrence risks for supraventricular tachycardias have been estimated at 50%, atrial fibrillation or flutter 52% and ventricular tachycardia 27%[37]. Adverse fetal events have been associated with antipartum arrhythmias.

Superventricular tachycardia may occur in the absence of structural heart disease, but in one study 53% of patients had underlying heart disease[37,40]. Tachycardia may be atrial or superventricular, and patients may already be on medications during pregnancy. If the patient has been relatively asymptomatic, a trial off mediation could be implemented during the first trimester; however, if the superventricular episodes have been at rather fast rates, ablation prior to pregnancy should be a consideration. It is possible that the superventricular tachycardia could recur with pregnancy with rapid rates and require additional medical therapy which could be problematic[11,12,41]. Wolff-Parkinson-White syndrome is associated with superventricular tachycardia, and it has been recommended that those patients should either continue their medications or consider ablation prior to pregnancy[38]. Atrial fibrillation and flutter is usually associated with underlying structural heart disease. Patients may require anticoagulation that needs to be continued at low dose throughout the pregnancy. During the first trimester patients should be changed to heparin. In the setting of atrial fibrillation during pregnancy, 96% of patients present with underlying structural heart disease[37].

Ventricular arrhythmias may also have occurred prior to pregnancy. This may occur in the setting of a structurally normal heart; although in one study in women with pre-existing ventricular tachycardia, 55% had underlying structural heart disease[37,42]. This condition may require continued therapy throughout the pregnancy. If an automatic implantable defibrillator is present, antiarrhythmic medication is necessary to prevent the device from firing[11,12,41]. In a recent study treatment of prolonged QT syndrome with beta blockade was found to decrease cardiac events (ventricular arrhythmias) in the postpartum period for up to 9 months[43].

MYOCARDIAL DISEASE

Women of childbearing age may have acquired myocardial disease. Depending upon the type of myocardial disease, pregnancy may be

contraindicated. For example, if systolic dysfunction is present and the ejection fraction is less than 40%, pregnancy is contraindicated[44]. All women who have underlying myocardial dysfunction require a full evaluation prior to pregnancy. This may include stress testing to assess functional ventricular reserve. Evaluation may be performed off medication, as the medication would optimally be best withheld in the first trimester in pregnancy. Medication could then be resumed later in pregnancy, but certain medications often used to treat women with myocardial disease may be contraindicated during pregnancy.

CORONARY ARTERY DISEASE

Atherosclerotic coronary artery disease is rare in women of childbearing age, except perhaps for female diabetics or those with familial hypercholesterolemia. Little current information is available regarding the preconceptional evaluation of women with coronary disease. Regardless, it is important to rule out active or potentially active coronary lesions and to ensure that the woman has normal ventricular function both at rest and with exercise[45]. It is also important to document the absence of ischemia during exercise. With these conditions met, pregnancy can take place with very careful monitoring throughout. For women who have had prior stenting, aspirin may be continued during pregnancy, although there is a risk of early ductal closure. Plavix has not been widely used during pregnancy and may be problematic.

DILATED CARDIOMYOPATHY

A woman of childbearing age may have a dilated cardiomyopathy due to a prior viral illness or to a prior pregnancy. In the setting of a dilated cardiomyopathy with reduced ejection fraction, pregnancy is contraindicated. However, it becomes more controversial if a woman has recovered from pregnancy followed by a peripartum cardiomyopathy[44]. If her ejection fraction remains reduced, she has a risk of clinical deterioration and death[44]. It is important to observe cardiac reserve, preferably off medication, with stress echocardiography. If a patient has not recovered from a peripartum cardiomyopathy, she remains at risk for recurrence and further deterioration[46]. Women who have received anthrocyclin therapy and/or radiation to the chest for childhood malignancies may have a cardiomyopathy as an adult. In a woman with this history, it is important to evaluate ventricular function and reserve very carefully prior to pregnancy using stress echocardiography. There may also be an underlying radiation induced vasculitis. There have been case reports of pregnancy after cardiac transplantation, at times occurring after peripartum cardiomyopathy. In addition to ventricular function, immunosuppressive medications and their potentially harmful effects on the fetus need to be considered[47,48].

HYPERTROPHIC CARDIOMYOPATHY

It is rare that a woman with hypertrophic cardiomyopathy develops heart failure with pregnancy. Symptoms occurring during pregnancy usually occur in women who have experienced symptoms prior to pregnancy, and pregnancy is often well tolerated[49]. In one study there were no increased arrhythmia rates in pregnancy compared to a non-pregnant control with hypertrophic cardiomyopathy. On the other hand, congestive heart failure has been described in women with hypertrophic cardiomyopathy, particularly in women who have a family history of hypertrophic cardiomyopathy[50].

RISKS TO FETUS

Risks to the fetus include prematurity, low birth weight and an increased risk of congenital

heart disease. The overall risk of congenital heart disease probably ranges between 4 and 10%[10]. The risk of congenital heart disease is higher if there is maternal or paternal outflow tract lesions such as aortic stenosis or coarctation of the aorta.

The preconceptional evaluation should begin with a very careful history to identify current symptoms or problems which could denote cardiac dysfunction. A complete history of prior surgeries must be obtained and the sequelae of such surgeries documented in detail. Next, a complete medication history is required to identify medications that need to be changed in anticipation of conception or to be withheld for the first 13 weeks when organ development is occurring. The issue of coumadin therapy and risk of embryopathy in the first trimester is complex and described elsewhere.

Family history is important to identify members of the family with congenital heart disease or a history of sudden death. It is important to understand the patient's level of activity in the course of her normal day. The ability to exercise and the type of exercise performed should be documented to provide an overall understanding of the functional capacity and how pregnancy may be tolerated. Medical problems that would affect the patient's cardiac status during pregnancy should be identified and treated, including as anemia, thyroid disease, smoking, alcohol abuse and illicit drug use[4]. Advanced maternal age may play a role with respect to coronary artery and cardiomyopathy risk.

Appropriate diagnostic testing is necessary as part of the preconceptional evaluation, and recommendations are summarized in Table 4. Electrocardiographic testing includes a 12-lead electrocardiogram or arrhythmia monitoring with a Holter monitor for brief periods of time or an event monitor. Echocardiography is important to identify the structure of the heart, valvular disease and shunt lesions, which can be further identified by contrast bubble studies. Echocardiography combined with stress testing is useful to assess functional reserve. Cardiopulmonary testing may be performed to assess aerobic threshold. Cardiac catheterization may be indicated to better define pulmonary pressures prior to pregnancy and to identify a woman who may benefit from a catheter-based intervention.

Table 4 The preconceptional evaluation for common cardiac lesions

	Testing modalities						
Lesion	*Exam*	*CXR*	*ECG*	*Echo*	*MRI*	*Stress test*	*Holter*
ASD	✓			✓			
VSD	✓		✓	✓			
Aortic stenosis	✓		✓	✓		✓	
Coarctation of aorta	✓		✓	✓	✓		
Tetralogy of Fallot	✓	✓	✓	✓		✓	✓
TGA – arterial switch	✓	✓	✓	✓		✓	✓
TGA – atrial switch	✓	✓	✓	✓	✓	✓	✓
Fontan	✓	✓	✓	✓	✓	✓	✓
Ebstein's anomaly	✓	✓	✓	✓		✓	✓
Dilated cardiomyopathy	✓	✓	✓	✓		✓	✓
Hypertrophic cardiomyopathy	✓		✓	✓	✓	✓	✓

CXR, chest X ray; ECG, electrocardiogram; Echo, echocardiogram; MRI, magnetic resonance imaging; ASD, atrial septal defect; VSD, ventricular septal defect; TGA, transposition of great arteries

Counseling the patient and her family

A total risk assessment needs to be formulated, depending on the nature of the cardiac lesion. This risk assessment may include a complete preconceptional evaluation to look for potential problems that may require attention prior to becoming pregnant. Medications may need to be altered in anticipation of pregnancy and interventions may need to be performed.

The potential risks of pregnancy, labor and delivery should be discussed with the patient and her family in the preconceptional evaluation. The frequency and monitoring of the tests that will be used to follow the patient should also be discussed. For example, that the patient may require hemodynamic monitoring for 24–28 hours after delivery in an intensive care setting to assess volume shifts should be discussed. The patient should understand that she may be physically separated from her child during that time. Other potential considerations at the time of labor and delivery can also be discussed, but not all complications can be fully anticipated.

In higher risk women, subsequent pregnancies also require full evaluation. It cannot be assumed that because a woman has had a successful pregnancy that her next will be equally uncomplicated. Full and complete evaluation must be undertaken prior to every pregnancy; and this discussion also should include the instruction to prevent pregnancy during the time of evaluation and intervention.

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4

Respiratory diseases in pregnancy: asthma

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During pregnancy, hormonal, immunological and physiological adaptations alter the course of many respiratory diseases. In addition, many respiratory illnesses produce significant negative effects on maternal and fetal outcomes.

Among pregnant women, the most common respiratory disease by far is asthma, with a prevalence ranging from 3.8 to 8%[1–5]. This illness is becoming an increasing concern, as its prevalence has increased among all women over the past decade[2,6,7]. Because of this, this chapter focuses on the diagnosis and management of asthma and its effect on pregnancy.

PREVALENCE, EPIDEMIOLOGY AND PATHOPHYSIOLOGY

In the United States alone, an estimated 14–15 million people have been diagnosed with asthma[2,6,7]. During childhood, the ratio of males to females is 2 : 1, whereas by adulthood the gender difference is no longer present. Regardless of gender or patient age, the health consequences of asthma are profound. Each year, complications of asthma account for 5000 deaths in the US. According to the Center for Disease Control and Prevention, patients with asthma collectively account for a total of 100 million days of restricted activity and 470,000 annual hospital admissions. Of particular note, adverse outcomes are not equally distributed, with disproportionate effects in African-Americans who have the greatest rates of hospital admission and asthma-related deaths among those aged 15–24[2,6,8].

Symptoms of asthma result from a combination of inflammation, edema and bronchospasm. Certain individuals appear to have a genetic predisposition that results in IgE production in response to various stimuli. IgE antibodies bind to mast cells and basophils, leading to the release of mediators including histamine, leukotrienes and cytokines, which in turn stimulate smooth muscle contraction, leading to narrowing of airway passages. Activation of cytokines promotes tissue inflammation, which both narrows bronchial airways and increases airway hyperresponsiveness[9].

Histologically, examination of the airways reveals denuded epithelium, edema and collagen deposition beneath basement membranes that leads to sub-basement fibrosis. Also seen is inflammatory cell infiltration with eosinophils, neutrophils and type 2 lymphocytes[9].

DIAGNOSIS

The signs and symptoms of asthma differ from patient to patient, and their severity may also vary in any given patient at different times. The following components are required for the diagnosis of asthma:

- Episodic symptoms of airflow obstruction
- Airflow obstruction that is at least partially reversible

- Absence of alternative diagnoses to explain symptoms.

Asthma symptoms may remit spontaneously or may require medical therapy. Common symptoms include coughing, wheezing, shortness of breath and chest tightness. In general, symptoms are worse at night and during early morning and improve during the day.

To make a diagnosis of asthma, a detailed history and physical examination should be performed to identify the following signs and symptoms:

- Hyperexpansion of the thorax
- Expiratory wheezing
- Severe rhinitis
- Nasal polyps
- Atopic dermatitis or eczema.

In addition, patients with newly diagnosed asthma should undergo spirometric evaluations or pulmonary function tests (PFTs) before and after inhaling β2 agonists in order to demonstrate reversible airway obstruction. Hand-held peak flow assessments should be used to monitor asthma symptoms, but should not be used to make the initial diagnosis[9,10].

Asthma is categorized according to the frequency and severity of symptoms and the results of PFTs[6,7,11]. Assignment of a diagnostic category is important because it helps predict prognosis, both prior to and during pregnancy, and guides initial selection of pharmacotherapy[8,9,12–16].

Mild intermittent asthma is characterized by fewer than two daytime exacerbations per week, and two or fewer night-time exacerbations per month. Exacerbations tend to be brief, lasting from a few hours to a few days. On formal PFTs, the forced expiratory volume in 1 second (FEV1) should be greater than or equal to 80% of expected value. There should be less than 20% variability of peak expiratory flow rate.

Mild persistent asthma is characterized by two or more daytime exacerbations per week, but less than one exacerbation per day, and two or more night-time exacerbations per month, but less than one exacerbation per week. Exacerbations may affect a person's level of activity. On PFTs, the FEV1 is still greater than or equal to 80% of expected value, but there is 20–30% variability of peak expiratory flow rate.

Moderate persistent asthma is characterized by daily daytime symptoms and at least one night-time exacerbation per week. These exacerbations are generally longer in duration, often lasting days, and may affect a person's level of activity. PFTs reveal an FEV1 60–80% of expected value, and greater than 30% variability of peak expiratory flow rate.

Severe persistent asthma is characterized by continuous daytime symptoms and frequent night-time exacerbations. These patients often have a chronically limited level of activity due to frequent exacerbations. PFTs reveal an FEV1 less than 60% of expected value and greater than 30% variability of peak expiratory flow rate.

The patient's 'triggers' for exacerbation(s) should be identified as part of the diagnostic work-up. These can include environmental allergens, upper respiratory infections, occupational exposures, medications (notably aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs)), exercise and emotional stress. The avoidance and control of triggers is discussed in the 'Management of asthma during pregnancy' section of this chapter.

EFFECTS OF PREGNANCY ON ASTHMA

Epidemiology

Although it is commonly stated that asthma improves during pregnancy in one-third of women, worsens in one-third of women, and remains unchanged in one-third of women, several studies have demonstrated that the

severity of asthma preconceptionally and during early pregnancy is predictive of the clinical course during the remainder of the pregnancy[3,17]. Women with mild asthma are less likely to require hospitalization, unscheduled office visits, oral steroids or experience exacerbations compared with women with moderate or severe asthma. Accordingly, among women with mild pre-pregnancy asthma, only 8–13% experience deterioration, and only 2% require hospitalization. In contrast, approximately 26% of women with moderate pre-pregnancy asthma deteriorate, and 7% require hospitalization. Among women with severe asthma prior to onset of pregnancy, 52–65% will develop a worsening of asthma symptoms, with 27% requiring hospitalization[3,8,16,18–20].

Other factors also predict which women are at greater risk of worsening of their asthma during pregnancy. Asthma symptoms tend to correlate with rhinitis symptoms, and women with more significant symptoms during pregnancy experience more asthma exacerbations as well[19]. Pregnant African-American women with asthma tend to have higher asthma-related morbidity than pregnant Caucasian women with asthma, independent of socioeconomic status[8]. Additionally, women pregnant with female fetuses experience more severe asthma symptoms than women pregnant with male fetuses[21,22]. It has been postulated that the surge in androgens at 12–16 weeks' gestation produced by male fetuses has a protective effect on maternal asthma.

With all three types, the severity of asthma symptoms reverts to pre-pregnancy levels within 3 months of delivery.

Pathophysiology

The hormonal, immunological and physiological changes of pregnancy affect the symptoms as well as the severity of asthma. Importantly, however, no pregnancy-related changes are seen in the FEV1, the ratio of FEV1 to vital capacity, or peak flow in patients with asthma; this stability means that criteria for diagnosis and monitoring of asthma do not change[9,23,24].

A number of pregnancy-related changes may act to ameliorate the course of asthma. For example, progesterone increases dramatically during pregnancy. This hormone acts as a smooth muscle relaxant, which may explain improved symptoms in some patients. Furthermore, both progesterone and estrogen potentiate β-adrenergic bronchodilation. Increased relaxin levels also promote relaxation of bronchial smooth muscle. At the same time, plasma histamine is decreased during pregnancy due to an increase in circulating histaminase. This may lead to a decrease in histamine-mediated bronchoconstriction. Further, pregnancy-related increases in circulating cortisol may produce anti-inflammatory effects, and circulating glucocorticoids may also increase β-adrenergic responsiveness, potentially improving the efficacy of some medications. Other changes that may promote bronchodilation and bronchial stabilization include increased levels of prostaglandin E2, prostaglandin I2 and atrial natriuretic factor[1,18,24–26].

At the very same time, however, competing pregnancy-related factors may exacerbate the course of asthma. Functional residual capacity (FRC) is decreased due to diaphragmatic elevation of up to 4 cm. This phenomenon may result in airway closure during tidal breathing and may alter ventilation–perfusion ratios. Competitive binding of progesterone, aldosterone and deoxycorticosterone to glucocorticoid receptors may decrease the anti-inflammatory effects of both endogenous and exogenous glucocorticoids. Increased prostaglandin F2α may promote bronchoconstriction, and placental-derived major basic protein (MBP) may increase immunologic sensitization[1,3,4,19,24–26].

In addition to these cited physiological changes, certain asthma triggers are either more common or more stimulatory in pregnancy. Some pregnant women experience

increased sensitivity to viral and bacterial respiratory tract infections. There may also be a marked increase in gastroesophageal reflux, often an asthma trigger[26–28]. Increased emotional stress can also increase the frequency of asthma exacerbations[15,29]. Finally, increased progesterone levels result in centrally mediated hyperventilation, manifested as 'dyspnea of pregnancy', or an increased patient sense of shortness of breath[18,25]. This latter circumstance may result in more patient complaints of respiratory symptoms, even in the absence of worsening asthma.

As with non-pregnant women, cigarette smoking increases the frequency of exacerbations[12]. Interestingly, the same may be said regarding excessive weight gain[30]. Furthermore, pregnant women often worry about effects of their asthma medications, and may discontinue them inappropriately. The complex interaction of all of the above factors in each individual patient determines whether asthma will improve, worsen, or remain stable during gestation.

EFFECTS OF ASTHMA ON PREGNANCY

Older, retrospective data had suggested associations of asthma with a host of poor pregnancy outcomes including hyperemesis, gestational diabetes, hypertension/pre-eclampsia, puerperal hemorrhage, cesarean delivery, preterm birth, intrauterine growth restriction, congenital malformations, perinatal mortality and stillbirth[16]. In contrast, recent prospective studies contradict this generalization. Indeed, the more recent data suggest that most women with asthma will have an uneventful pregnancy course[31–33]. For women with well controlled asthma, pregnancy outcomes are similar to those of women without asthma[26,31–34].

This having been said, and in line with comments earlier in this chapter, women with more severe or poorly controlled asthma are prone to adverse perinatal outcomes. One study showed statistically significant increases in gestational diabetes, small for gestational age newborns and cesarean delivery for women with moderate–severe asthma, even with optimal control, when compared to controls without asthma[35]. Women with daily symptoms also had higher rates of pre-eclampsia[36]. Need for oral steroids was independently predictive of delivery prior to 37 weeks and low birth weight (less than 2500 g)[35,37]. Pulmonary function testing was also predictive of pregnancy outcomes: an FEV1 less than 80% of predicted values was associated with preterm delivery, pre-eclampsia, cesarean delivery and small for gestational age newborns[1,32,35].

Importantly, management by a physician with experience in asthma, such as a pulmonologist or perinatologist, decreases the risk of perinatal mortality, preterm birth and low birth weight in women with moderate to severe asthma[11]. Unfortunately, similar management has not been shown to be beneficial in decreasing the risk of pre-eclampsia in pregnant women with asthma. Women with acute exacerbations requiring emergency room visits or hospitalization should be managed collaboratively by the emergency physician or pulmonologist and the obstetrician[11].

MANAGEMENT OF ASTHMA DURING PREGNANCY

A detailed history and physical examination should be performed to identify signs/symptoms of asthma during the initial encounter with the patient. Optimally, this assessment should occur prior to conception in order to establish a baseline[1]. Patients who have not had a baseline status established prior to pregnancy should have it established at their first obstetric visit[34,38].

A detailed history of disease status during prior pregnancies should be elicited because asthma symptoms experienced during prior pregnancies are generally predictive

of symptoms experienced in subsequent pregnancies in any given patient[16,19,35]. Patients should be encouraged to take an active role in their disease management, paying close attention to factors which affect their disease status and the onset of exacerbations[39,40]. This includes the avoidance of potential triggers, particularly cigarette smoking and recognizing the impact of excessive weight gain during pregnancy[7,12].

Management or co-management of these patients by a physician with sufficient experience in caring for pregnant asthmatics improves outcome[34]. The following criteria should be used to guide decisions about referrals. Patients who experience a life-threatening exacerbation; fail to meet treatment goals; exhibit atypical or severe persistent symptoms or with an unclear diagnosis; present as candidates for immunotherapy; require continuous systemic corticosteroid therapy or more than one short course of corticosteroids per year; or have complicating symptoms including nasal polyps, gastroesophogeal reflux disease (GERD), severe rhinitis, or chronic obstructive pulmonary disease (COPD) all will benefit from early and/or urgent referral[7,11,39–41].

Women who experience acute asthmatic exacerbations during pregnancy should be managed similarly to women with asthma who are not pregnant. Asthma exacerbations tend to be most common between 24 and 36 weeks' gestation, at which time patients should be advised to be proactive in the management of their disease[11,23,24,32]. Mild to moderate respiratory symptoms should be recognized and treated as aggressively as if these women were not pregnant with the recognition that the evolution to a more serious condition has the potential to worsen maternal as well as fetal status. Fewer acute exacerbations are reported to occur after 37 weeks' gestation and exacerbations are also uncommon during labor. However, and most importantly, women with inadequately controlled symptoms prior to labor are more likely to have exacerbations during labor[4,24,31–34,42].

Establishing patient-centered treatment goals

In order to engage the patient in monitoring and treating her own disease, as well as to determine when therapy is inadequate and requires escalation or augmentation, it is critical to establish specific goals at the outset of treatment. Treatment goals should be geared towards the prevention of chronic symptoms, and/or exacerbations, and maintenance of normal activity level[6,7,41]. An effective medication regimen with as few side-effects as possible should be prescribed.

Treatment algorithm[7,10,11,23,31–34,37,41]:

1. Patients should be educated on how to perform accurate peak flow measurements. They should establish with their physician their personal best baseline peak flow measurement which is used to compare future values:
   a. 'Typical' peak flow in pregnancy: 380–550 l/min
   b. Green zone: >80% of personal best
   c. Yellow zone: 50–80%
   d. Red zone: <50%.
2. Follow-up evaluations of pulmonary function can be accomplished with peak-flow measurements.
3. All pregnant women with asthma should receive a written action plan describing the management of acute and chronic symptoms.
4. Patients with mild persistent disease should monitor peak flow values monthly. Patients with moderate–severe disease should be counseled to do daily peak flow evaluations. All patients should evaluate peak flow values during an exacerbation.

5. Patients should be educated on how to perform accurate peak flow measurements. They should establish with their physician their personal best baseline peak flow measurement which then can be used to compare to future values. The 'typical' peak flow in pregnancy ranges from 380 to 550 l/min. If patients find that their peak flow is between 50 and 80% of their personal best, they should follow additional steps, depending upon whether their peak flow is above or below 50% of their personal best.
6. Patient should immediately notify physicians of any red zone values and the patient should have a prescribed action plan.
7. Patients with repeated values in their yellow zone may require an escalation of therapy at their next office visit.
8. Chest radiographs should be used to evaluate patients with exacerbations to rule out infection and other disease processes.
9. Serial ultrasound surveys for growth should be performed during the third trimester for patients with poorly controlled asthma and/or baseline moderate–severe persistent disease requiring chronic oral corticosteroid therapy.
10. Additional testing (non-stress test) may be considered based on asthma severity or evidence of fetal growth restriction.

Management of labor and delivery

Scheduled asthma medications should be continued during labor and delivery. Patients on systemic steroids should receive stress dose steroids at the time of delivery and for up to 24 hours postdelivery[27,37]. Indomethacin should be used with caution in patients with NSAID-induced asthma symptoms because of its potential to cause bronchospasm[42]. Morphine and meperidine should be used with caution, given that these medications stimulate histamine release that can worsen asthma symptoms[27].

Although some prostaglandins (PG) may worsen asthma symptoms, this effect is not universal, and the individual properties of each prostaglandin should be considered when making decisions with regards to their use in patients with asthma. For example, PGE1 (misoprostol) induces airway dilation while decreasing inflammation and cellular proliferation; as such it is not contraindicated in pregnant asthmatics. PGE2 (dinoprostone) is a potent bronchodilator and also is not contraindicated in such patients. On the other hand, PGF2α (carboprost) may trigger airway constriction, inflammation and vasoconstriction and thus should be used with caution in women with asthma[9,25,43].

ASTHMA TRIGGERS AND COMORBIDITIES

The identification and avoidance of triggers is important in optimizing asthma management both during and outside of pregnancy. A number of triggers should be considered and it is important to remember that more than one may be operative in any given patient.

Infections

Respiratory infections are the most common triggers of asthma exacerbations, accounting for as many as 60% of all asthma-related hospital admissions. Colonization of the upper respiratory tract by pathogens leads to cell-mediated inflammatory processes, which in turn lead to bronchoconstriction. Individuals with asthma are more susceptible to colonization by infectious agents and experience slower rates of pathogen clearance. Effects from infection

-related exacerbations may last up to 8 weeks after the primary infection[19,28,32,43].

Viral infections are more commonly associated with asthma exacerbations than bacterial infections and should be considered in all patients experiencing exacerbations. In adults, rhinovirus is most commonly associated with exacerbations. Co-infection with influenza virus is also common in individuals experiencing exacerbations. Accordingly, all women who expect to be pregnant during the influenza season should be offered influenza vaccination[28].

Drugs

Drug-induced exacerbations most commonly are due to aspirin or cyclooxygenase-1 (COX-1)-inhibiting NSAIDs. The prevalence of NSAID-induced respiratory symptoms is 10–11% in asthmatics compared to 2.5% in non-asthmatics. NSAID-induced asthma is thought to be caused by an inhibition of COX-1 in the airway of sensitized patients which results in a depletion of PGE2, a potent bronchodilator. As a result, patients with asthma may experience bronchoconstriction after exposure to these agents[23,26,27,43].

Highly selective COX-2 inhibitors may not exhibit the same bronchoconstrictive properties and, thus, may present a reasonable alternative if clinically indicated. In individuals for whom there is no alternative therapy to COX-1, it is possible to offer desensitization to COX-1 inhibitors. Medications such as acetaminophen and sodium salicylates are generally well tolerated and typically do not act as triggers for asthma symptoms[23,26,27,43].

Occupational triggers

Occupational triggers account for 5% of all asthma complaints and 26% of all work-related respiratory disease. Occupational induced asthma exacerbations are characterized by temporal as well as cyclic trends. Typically, upon arrival to work these individuals are symptom-free. As the work day continues, symptoms develop and become progressively worse only to remit or lessen after these individuals leave the work place. Remission is notable during holiday and vacation time, but resumption of work initiates the cycle anew[9,13].

Common occupational triggers include metal salts, wood products, residues from grain products and a variety of industrial chemicals. Exposure to these agents induces both an early and a late response, both of which are mediated by mast cell activation. Early responses are a result of histamine and leukotriene release resulting in bronchoconstriction. Late responses are a consequence of cytokine and chemokine production, which leads to inflammation of the tracheobronchial airway. Differences in the pathophysiology of these responses should be considered when deciding upon appropriate therapy[9,11,13].

Exercise-induced asthma

Exercise-induced asthma is characterized by acute bronchoconstriction during or immediately after exercise. Fifty to 90% of all asthmatics experience airway sensitivity related to physical activity. Clinically, exercise-induced asthma is defined as 10% or more decline in FEV1 following exercise. During exercise, the increase in inspired air overwhelms the body's ability to warm the air to body temperature prior to its reaching the distal airways. Bronchoconstriction is the result of cold (unwarmed) air reaching the distal bronchial tree[14].

Environmental allergens

Hypersensitivity responses to environmental allergens require prior extended exposure to the offending agent to produce sensitization.

Individuals who are sensitized to a particular agent mount an IgE-mediated response after which subsequent reintroduction to the agent leads to histamine production, which causes rhinitis and progressive bronchoconstriction.

Environmental allergenic triggers frequently follow seasonal patterns and 75–85% of asthmatics have positive skin tests to common environmental allergens. Environmental triggers include indoor and outdoor exposures. Outdoor triggers are usually related to climate conditions that promote increases in agents such as ozone, nitrogen dioxide and sulfur dioxide often resulting in respiratory symptoms in the general population. Often, however, the asthmatic population experiences an exaggerated response to subtle atmospheric changes. Indoor triggers include exposure to animals, tobacco smoke, dust mites, molds and cockroaches, and as such often are implicated in the development of childhood asthma. Activities that may be taken to lessen these symptoms include the removal of carpets/rugs, reduction of humidity in an effort to decrease mite growth, departure from the house during vacuuming, weekly bathing of pets (or removal of pets) and the control of cockroaches[1,12,23,33].

Emotional stress

Asthmatic patients experience changes in elastic recoil, ventilation distribution and pulmonary blood flow during times of high stress. Positive and negative emotional stresses stimulate vagal efferent activity, inducing changes in airway hyperactivity in some patients. These changes influence airway resistance by modifying smooth muscle contractions and respiratory secretions[15].

PHARMACOTHERAPY

Most medications used for asthma treatment outside of pregnancy are also not contraindicated during pregnancy. Below, we provide a discussion of the mechanism of action of each class of drug, special considerations for use during pregnancy, and specific examples of medications with their FDA classification for use in pregnancy[9,17,23,32,38]. Table 1 describes the FDA classification system for medications in pregnancy.

β_2 agonists

β_2 agonists bind to β_2 receptors on bronchial smooth muscles increasing cyclic AMP production, leading to bronchial relaxation and dilation. β_2 agonists also inhibit the release of mediators of immediate hypersensitivity from mast cells. They can be further classified as short acting agents used for acute exacerbations, and long acting agents used for maintenance therapy in patients with moderate to severe persistent disease[5,9,17,36].

Table 1 FDA pregnancy classification of medications

Risk category	*Animal data*	*Human data*	*Recommendation*
A	Negative	Negative	Use approved
B	Negative	None available	Use approved
B	Positive	Negative	Use approved
C	Positive	None available	Use approved
C	None available	None available	Use approved
D	Positive/negative	Positive	Use approved
X	Positive	Positive	Contraindicated

Short acting agents are considered first line therapy for the management of acute exacerbations as well as for patients with mild intermittent disease. Short acting β_2 agonists should not be used for maintenance therapy. These agents are not contraindicated during pregnancy or lactation and have not been associated with an increased risk of congenital malformation or adverse pregnancy outcome.

Long acting agents are best for patients with moderate to severe persistent disease who are not adequately controlled with inhaled steroids alone. Although human data are scant, they lack any evidence of an increased risk of congenital malformations. Risk–benefit considerations favor the use of these medications in select patient groups[5,9,17,36].

Examples include:

- Short acting: albuterol (category C)
- Long acting: salmeterol (category C).

Inhaled corticosteroids

Inhaled corticosteroids counteract the inflammatory response that takes place during asthma exacerbations. In addition, inhaled corticosteroids act to modify the immune response by inhibiting the activation of numerous cell types including mast cells, eosinophils, neutrophils, macrophages and lymphocytes.

Inhaled corticosteroids should be initiated as maintenance therapy in patients with persistent asthma symptoms. They are not contraindicated in pregnancy and have not been associated with an increased risk of congenital malformation or adverse pregnancy outcome[5,17,35,43].

Examples include:

- Beclomethasone (category C)
- Budesonide (category B)
- Fluticasone (category C)
- Flunisolide (category C).

Systemic corticosteroids

As with inhaled corticosteroids, systemic corticosteroids act as anti-inflammatory agents to reverse the inflammatory response characteristic of asthma exacerbations. They also modify the body's immune response to stimuli by inhibiting the activation of numerous cell types including mast cells, eosinophils, neutrophils, macrophages and lymphocytes[5,9,35,36].

A number of clinical studies have found an association between chronic systemic steroid use during pregnancy and adverse pregnancy outcome including preterm delivery, preeclampsia and intrauterine growth restriction. However, it is not clear to what extent these outcomes are related to the disease process *per se* and not to the drugs used to treat it. For example, reports suggest that infants of mothers treated with corticosteroids during the first trimester have an increased risk of facial clefts (0.1–0.3%). Despite this, due to the documented increase in maternal and fetal morbidity and mortality associated with poorly controlled asthma, and the important role that systemic steroids may provide in asthma control, the American College of Obstetrics and Gynecology recommends that systemic steroids be used when clinically indicated and that benefits for maternal and fetal health are perceived to outweigh risks. Systemic steroids should be administered in short bursts for patients with severe asthma exacerbations. A select group of patients will require chronic use of systemic steroids to adequately manage asthma symptoms[5,9,23,35,36].

Examples include:

- Prednisone (category C)
- Methylprednisone (category C)
- Dexamethasone (category C).

Anticholinergics

Anticholinergics act by binding to acetylcholine receptors, thereby reducing the action of acetylcholine. This reduction in acetylcholine activity results in an inhibition of secretions from serous and seromucous glands and a reduction of symptoms associated with asthma exacerbations. These agents should be considered as add-on therapy to β_2 agonists for the treatment of acute asthma exacerbations. Anticholinergics have not been associated with an increased risk of congenital malformation or adverse pregnancy outcome[23,26,32,34,40].

Examples include:

- Ipatropium (category B).

Methylxanthines

Methylxanthines work by promoting smooth muscle relaxation. They also suppress the hypersensitivity reaction of the airways to stimuli. Theophylline, the most commonly used methylxanthine, is not commonly prescribed during pregnancy due to multiple drug interactions, the need to monitor levels and bothersome side-effects. Side-effects such as insomnia, heart burn, palpitations and nausea all decrease patient tolerability. It is, however, not contraindicated in pregnancy, as it has not been associated with an increased risk of congenital malformations or adverse maternal outcome[23,26,32,34,40].

These agents should be considered as add-on therapy to inhaled corticosteroids therapy regimens. To ensure efficacy and safety serum levels should be titrated and maintained to levels between 5 and 12 μg/ml.

Examples include:

- Theophylline (category C).

Cromoglycates

Cromoglycates block the activation of chloride channels which results in an inhibition of airway inflammatory cells including mast cells. Cromoglycates are effective in preventive therapy for individuals with persistent asthma.

Cromoglycates should not be used as a first line therapy as their efficacy is generally considered less than that of inhaled corticosteroids. Patients with mild persistent asthma who are effectively managed with cromolyn sodium prior to pregnancy may be maintained on their current regimens. Cromolyn sodium use has not been associated with an increased risk of congenital malformations or adverse maternal outcome[5,23,32,34,38].

Examples include:

Table 2 FDA recommendations for asthma therapy

Asthma classification	*Recommended therapy*
Mild intermittent	Inhaled β_2 agonist as needed
Mild persistent	1st scheduled inhaled corticosteroids 2nd scheduled inhaled cromolyn
Moderate persistent	Scheduled inhaled corticosteroids plus theophylline or salmeterol
Severe persistent	Scheduled inhaled corticosteroids plus theophylline or salmeterol plus oral corticosteroids prescribed in short bursts or daily dosing as needed

- Cromolyn sodium (category B)

Leukotriene inhibitors

Leukotriene inhibitors act to antagonize leukotriene activity, thereby inhibiting bronchial smooth muscle contractions as well as the reactive inflammatory response.

Leukotriene inhibitors are effective in mild–moderate asthma management. Information regarding the use of leukotriene inhibitors during pregnancy is limited, and they should only be used in patients with intractable asthma who require them for adequate symptom control. Zileuton should be avoided in pregnancy due to unfavorable results observed in animal studies that demonstrated increased rates of miscarriage, stillbirth, low birth weight and skeletal abnormalities associated with its use[5,23,32,34,38].

Examples include:

- Zafirlukast (category B)
- Montelukast (category B)
- Zileuton (category C – not recommended).

A summary of the current FDA recommendations for initiation of therapy is included in Table 2.

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5
Diabetes mellitus

Sandra Newbold and Helen Ward

Preconception counseling and care is as important for women with type 2 diabetes as it is for those with type 1, as the Confidential Enquiry into Maternal and Child Health (CEMACH) study of 2002–2003 (reported 2005) has shown poor outcomes in both groups[1]. However, the focus of care is slightly different in the two groups and always needs to be individualized. Diabetes is a common condition, which affected 3.75% of the population of the UK in 2006–7[2].

The increasing prevalence of type 2 diabetes mellitus among younger individuals is reflected in women of reproductive age. In our own combined obstetric and diabetes clinic no women with type 2 diabetes were encountered until 2003. However, by 2007 they accounted for 21% of the clinic population. The circumstances in our institution reflect the changes taking place in the general population, as also shown in the UK Northern Diabetes Pregnancy Survey, which recently reported a fourfold increase in the number of pregnancies in women with type 2 diabetes when they compared data for 2002–2006 to those obtained between 1996 and 2001[3].

In an ideal world women with diabetes will have planned pregnancies and the opportunity for appointments before stopping contraception, and for preconception counseling and care with a multidisciplinary team that includes a diabetes nurse and dietitian in addition to an obstetrician and diabetes physician. Although the evidence is clear that pre-pregnancy planning is beneficial for these women, at present a high percentage of pregnancies in the UK are unplanned[4,5]. As a result, many women with diabetes do not receive optimal pre- and early pregnancy care, leading to an adverse effect in 51% of those in the 2006 CEMACH study reporting unplanned pregnancy[6].

Pre-pregnancy assessment of women with diabetes allows the following areas, discussed below, to be addressed:

- Glycemic control
- Insulin analogues
- Drugs
- Complications of diabetes
- Effect of pregnancy on diabetes
- Breastfeeding
- Effect of diabetes on pregnancy
- Effect of diabetes on the neonate.
- Risks of inheriting diabetes.

GLYCEMIC CONTROL

For women with diabetes mellitus, an elevated glycated hemoglobin (HbA_{1C}) is associated with increased risks of adverse pregnancy outcome including miscarriage, congenital anomalies and stillbirth. Because these risks increase when the HbA_{1C} rises above 7% in the preconception and early pregnancy period[7], women are encouraged to achieve as near normal glycemic control as possible, with the

recent National Institute for Health and Clinical Excellence (NICE) guidelines suggesting a target preconception HbA_{1C} of 6.1%[8]. The American Diabetes Association (ADA) recommendations for care recommend a target HbA_{1C} of less than 6.0%[9]. Suhonen and co-workers report a relative risk for fetal malformations of 3.0 for women with type 1 diabetes with marginally elevated HbA_{1C} (5.6–6.8%)[10], with the association still present after adjusting for other factors including maternal age, duration of diabetes, parity and smoking. Another study stratified women with type 1 diabetes into two groups based on an initial HbA_{1C} above or below 7.5% and found a four-fold increase in adverse outcomes along with a nine-fold increase in congenital anomalies in the group with higher HbA_{1C}[11]. Although the 1989 St Vincent Declaration aimed for 'a pregnancy outcome in the diabetic woman that approximates to that of a non-diabetic woman'[12], the 2005 CEMACH data documented much higher rates of stillbirth, perinatal death and neonatal death than national rates for diabetic women in the UK, with equally poor rates being observed for types 1 and 2[1]. These findings underscore the compelling need for further improvement in outcomes.

NICE recommends that conception be avoided if glycemic control is very poor as indicated by an HbA_{1C} of greater than 10%[8]. This recommendation is based on the marked increases in congenital anomalies that accompany increases in HbA_{1C}. For example, Greene and colleagues reported a more than 12-fold increased relative risk of a congenital anomaly associated with an HbA_{1C} of greater than 12.7% compared with below 9.3%[13]. Accompanying this, significantly higher rates of spontaneous abortion also are observed once the HbA_{1C} is greater than 12%[14].

Preconception counseling and care *per se* are associated with improved outcomes for diabetic women. In a meta-analysis the rate of congenital anomalies was 2.1% in women who received preconception care in comparison to 6.5% in those who had not[5]. However, these data need to be interpreted carefully, as women who access preconception care tend to be older, less likely to smoke and have a lower HbA_{1C} in the first trimester. In contrast, those women who do not access preconception care are more likely to have had an unplanned pregnancy with its inherent risks.

One of the major components of preconception care is achieving and continuing to maintain optimal glycemic control, whilst taking into account each individual's situation with regards to her diabetes. To achieve the HbA_{1C} target recommended by NICE, the blood glucose ranges should be 3.9–5.5 mmol/l premeals and up to 7.8 mmol/l on a 1-hour postprandial reading[8]. Monitoring for postprandial hyperglycemia clearly improves pregnancy outcome[15]. Multiple daily blood glucose testing is essential to achieve the best possible glycemic control. In striving for near normal glycemic control prior to conception, it is essential that this be balanced against the risks of hypoglycemia and, in particular, severe hypoglycemic episodes. A severe hypoglycemic episode is described as one that requires assistance of another person. *A diabetic woman's risk factors for severe hypoglycemic events include previous severe episodes and known impairment or absence of hypoglycemic warnings*[16,17]. Hypoglycemia treatment and avoidance are discussed below. For those women who may be unable to achieve these extremely tight targets for whatever reasons, it is useful to be aware that each 1% reduction in HbA_{1C} achieved before conception is associated with improvements in outcome. Achieving an HbA_{1C} of below 7% without driving it lower may be more feasible for many women with longstanding diabetes, especially those on insulin[7].

For women with type 2 diabetes, it may be necessary to consider a transfer to insulin therapy to optimize their glycemic control before conception. Metformin is not licensed in the UK for use in pregnancy, but its continuation should be considered in those women

who are likely to have continued benefit from this agent, e.g. those with known insulin resistance or those likely to be insulin resistant due to obesity. This position is supported by the 2008 NICE guidelines and requires clear documentation of informed consent with respect to continued use of metformin during pregnancy[8]. Care should be taken to avoid sudden discontinuation of metformin without substitution with insulin if this results in hyperglycemia in early pregnancy. If good glycemic control can be achieved with metformin in combination with lifestyle measures (diet and exercise), then insulin initiation may not be necessary preconception, although the woman should be informed that she is likely to require insulin therapy during the pregnancy. Women with a body mass index greater than 27 kg/m^2 should see a dietitian if they have not already received dietary advice[8]. All diabetic women should be encouraged to take regular exercise both before and during pregnancy.

Sulfonylureas are usually avoided during pregnancy, although they are increasingly being used in gestational diabetes mellitus and are reported as being safe[18]. However, the usual practice in the UK is that they are discontinued and insulin substituted prior to pregnancy. All other oral antidiabetic agents should be stopped prior to conception, including thiazolidinediones (glitazones), meglitinide analogues, alpha-glucosidase inhibitors, GLP-1 analogues and gliptins. Transfer to insulin should be arranged promptly in the case of unplanned pregnancy in a woman with type 2 diabetes mellitus taking any of these agents, as their safety has not been formally assessed in pregnancy. In the absence of safety data, some people still use these agents.

INSULIN ANALOGUES

Insulin analogues were developed in an attempt to achieve similar pharmacokinetics following an insulin injection to those achieved with endogenously produced insulin. As insulin affects growth and gene expression in addition to having metabolic actions, the safety of insulin analogues has been studied carefully and their use in pregnancy has been approached with caution.

The rapid acting analogues insulin lispro and insulin aspart have advantages over conventional short-acting human insulin due to their shorter onset of action, earlier peak effect and reduced likelihood of hypoglycemic events due to their shorter duration of action[19]. These attributes make them ideal for use in pregnancy, as they can help avoid postprandial hyperglycemia combined with a lower risk of hypoglycemic events. Both lispro and aspart have similar outcomes in pregnancy in comparison with human insulin, with improved satisfaction and potential benefits with respect to observed hypoglycemia; their use in pregnancy is supported by both NICE in the UK and the American Diabetes Association (ADA) in the US[8,9,20,21].

This position is in contrast to that of the long-acting insulin analogues: insulin glargine and insulin detemir. Current guidelines (2008) from both NICE and ADA are that women should be transferred to isophane insulin, commonly known as NPH (neutral protamine Hagedorn) by the time of the first antenatal visit. These recommendations are made primarily because of insufficient patient safety data, although evidence is beginning to accrue supporting their use. Long-acting insulin analogues were designed to provide a longer duration of action with a less pronounced peak of action compared to isophane insulin. Insulin glargine and insulin detemir both have a duration of action of up to 24 hours[22,23]. Price and associates reported a group of 32 women treated with insulin glargine compared to matched controls treated with human insulin with no observed differences in birth weight, fetal macrosomia or neonatal morbidity[24]. A clinical trial comparing insulin detemir to isophane insulin in 400 pregnant women

with type 1 diabetes is currently in progress with an estimated completion date in 2010[25]. Women who have had previous problems with isophane insulin, especially nocturnal hypoglycemia, may be reluctant to transfer back to isophane insulin from a long-acting analogue insulin. In this situation, it may be appropriate to continue the analogue insulin if an informed decision is made balancing the benefits of improved glycemic control with less hypoglycemia versus an unquantified risk to the fetus.

DRUGS

Women with diabetes often take a range of medications prior to pregnancy. Ideally a preconception appointment with a multidisciplinary team allows these medications to be reviewed so that appropriate changes can be planned before conception occurs. Unfortunately, many conceptions are unplanned and this is not always possible.

From 1 to 6% of women of childbearing age have clinically diagnosed hypertension prior to pregnancy and are taking antihypertensive medication(s); many also have long-term diabetes[26]. In addition, many non-hypertensive diabetics are prescribed angiotensin-converting enzyme inhibitors (ACE inhibitors) for diabetic nephropathy. Ideally such drugs should be reviewed prior to conception to determine whether they should be continued, stopped or changed prior to pregnancy, or once it is confirmed. Parkinson reviewed the safety of antihypertensive drugs in pregnancy and concluded that there was no evidence of teratogenicity with methyldopa, beta-blockers, calcium channel blockers and hydralazine[27]. It is well known that ACE inhibitors are absolutely contraindicated in the second and third trimesters because they are known to cause fetal oliguria, which leads to oligohydramnios and its sequelae for the fetus[28]. Case reports suggest similar fetotoxicity with angiotensin II receptor antagonists, and animal studies have shown that angiotensin II receptor antagonists are associated with serious fetal anomalies[29]. A recent American study also suggested a teratogenic effect for ACE inhibitors: 7.12% of fetuses born to women taking ACE inhibitors at the time of conception had anomalies at birth compared to 2.63% of the population not exposed to antihypertensive medication in the first trimester[30]. Under these circumstances, women taking ACE inhibitors or angiotensin II receptor antagonists at the preconception assessment should be assessed to determine whether they should stop medication whilst trying to conceive or change to alternative drugs at this time. It is the authors' practice to continue all other antihypertensive medications whilst women are trying to conceive, then to review the need for continuation during pregnancy depending on the blood pressure at that time. When the midtrimester drop in blood pressure occurs, many hypertensive women do not need to continue treatment, but may need reinstitution later in the pregnancy. The usual practice in the UK is to use methyl dopa or labetalol for blood pressure control as these are the medications with which British obstetricians have the most experience.

Many diabetic women are prescribed statins to provide long-term protection against cardiovascular disease. Unfortunately, data on the use of statins in pregnancy are limited, and the manufacturers advise against their use at this time. However, the available evidence is far from conclusive, but since statin use is preventive rather than therapeutic the most sensible approach is to advise women to stop these drugs when they are planning to conceive and to restart them once they have finished breastfeeding[31].

Because folic acid supplements decrease the risk of neural tube defects (NTDs) and facial clefts, it is recommended that all (as opposed to only those who are diabetic) women take them for 3 months before stopping contraception and until 12 weeks into the pregnancy[32,33].

Many authorities, especially those in the US, recommend continuing folic acid throughout the remainder of the pregnancy. The need for the preconception administration is because the neural tube is closed by the 28th day of gestation and commencing folic acid after that date is without benefit, a fact which is often underappreciated in the wider medical community. The standard recommended dose of folic acid is 400μg/day, but women at high risk of NTDs are advised to take a higher dose (5 mg daily), leading to the NICE recommendation that women with diabetes take the higher dose[8].

Women with long-term diabetes are at greater risk of developing pre-eclampsia than the general population (see below), a point which favors prophylaxis to reduce the risks of this condition[34,35]. Unfortunately, the ideal agent to accomplish this task has not yet been determined[36]. Low-dose aspirin was investigated in the CLASP study and found to only slightly reduce the rate of pre-eclampsia[37]. A subsequent meta-analysis on the use of prophylactic antiplatelet agents (mainly low-dose aspirin) suggested a 10% decrease in relative risk of developing pre-eclampsia[38] and confirmed the safety of low-dose aspirin in pregnancy. If low-dose aspirin is to be used, it should be started once a woman has a positive pregnancy test and continued until 34 weeks, as per the CLASP protocol. Whereas the initial investigation of prophylactic high-dose vitamins C and E (antioxidants) appeared to protect against pre-eclampsia, the VIP trial did not confirm this, and showed some significant negative effects[39,40]. Calcium supplements are currently being investigated, and the results appear to be encouraging. A recent meta-analysis of 12 randomized controlled trials of calcium supplements showed a 52% reduction in the incidence of pre-eclampsia compared to placebo with no obvious evidence of harm[41]. The benefits appeared to be even greater in high-risk groups. At present in the UK, calcium supplements are not often used in clinical practice.

The prevention of toxemia is a complex issue and is discussed elsewhere in this volume.

COMPLICATIONS OF DIABETES

Preconception consultations are an ideal time to assess any diabetic complications along with working to achieve improved metabolic control. Baseline measurements of renal and thyroid function should be taken. As autoimmune thyroid disorders are more common in women with type 1 diabetes and even mild anomalies in thyroid hormone levels can impact early fetal development, it is essential to identify those requiring treatment[42].

Retinopathy

Diabetic retinopathy is a broad term encompassing all disorders of the retina caused by long-term high blood glucose levels. It is essential for all women with diabetes to have a retinal assessment prior to conception to determine whether ophthalmological treatment is required. The initial retinal assessment also provides a baseline for further monitoring during each trimester. Pregnancy and rapid improvement of glycemic control are both known to be associated with deterioration of retinal disease, and sudden improvement of glycemic control should therefore be avoided until after a retinal assessment has been undertaken[8]. Women with proliferative retinal changes require urgent referral for ophthalmologic review and should receive treatment prior to pregnancy.

The Diabetes Control and Complications Trial[43] confirmed that diabetic retinopathy can worsen during pregnancy but it is reassuring that no long-term consequences were demonstrated when this occurred. A prospective study of 139 women with pregestational type

1 diabetes demonstrated a progression of retinopathy in 5% of pregnancies and observed that this was more likely in women with a longer duration of diabetes (>10 years) and more advanced retinal disease at baseline[44]. Women should be reassured that laser photocoagulation can be used during pregnancy, but ideally treatments should be undertaken prior to conception.

Nephropathy

Nephropathy is a serious complication of diabetes that can lead to end stage renal failure in addition to poor pregnancy outcomes (see Table 1). In a retrospective analysis of stillbirths occurring in women with type 1 diabetes, a six-fold higher incidence of nephropathy was noted in the stillbirth group compared to the reference group (i.e. those without nephropathy)[45]. Assessment of renal function with serum creatinine, estimated glomerular filtration rate (eGFR) and urinary excretion of albumin prior to conception should be performed in all diabetic women prior to conception. The 2008 NICE guidelines recommend referral to a nephrologist if creatinine is greater than 120μmol/l or eGFR below 45 ml/min[8]. Optimal control of blood glucose and hypertension protects against development or progression of nephropathy both prior to and during pregnancy. As ACE inhibitors and angiotensin II receptor antagonists are commonly used for nephropathy outside pregnancy, a careful review of medication as described above is essential.

Table 1 Diabetic nephropathy and effect on pregnancy. Adapted from American Diabetes Association summary of evidence and consensus recommendations of care for managing pre-existing diabetes for pregnancy[9]

Level of albuminuria	*Effect on pregnancy*
Normal <30 mg/24 hours	Unknown
Microalbuminuria 30–300 mg/24 hours	Increased pre-eclampsia
Macroalbuminuria >300 mg/24 hours	Increased pre-eclampsia
Protein excretion >500 mg/24 hours	Increased risk of growth restriction

Measurement of urinary albumin excretion prior to or early in pregnancy gives an individual baseline for comparison later in pregnancy and enables identification of those women with microalbuminuria or overt diabetic nephropathy, both of which are associated with preterm delivery, mainly due to pre-eclampsia[46]. Pregnancy does not appear to have a negative impact on long-term renal function in women with diabetic nephropathy who have maintained a good level of pre-pregnancy renal function (normal levels of serum creatinine) in contrast to those with low creatinine clearance before pregnancy[47,48].

Other complications of diabetes

Data regarding changes in diabetic neuropathy during pregnancy are lacking. Sensorimotor neuropathy in women with diabetes rarely causes problems during pregnancy and does not appear to progress, but careful review of drugs used for control of neuropathic pain should be undertaken during preconception appointments because of the possibility of teratogenicity. Women with autonomic neuropathy can have particular problems during pregnancy. Autonomic neuropathy is associated with hypoglycemic unawareness, which can be aggravated by pregnancy. Management of hypoglycemia is discussed below. Patients who have developed gastroparesis as a component of autonomic neuropathy often have poor metabolic control and inadequate nutrition[49,50]. This complication is subsequently associated with adverse pregnancy outcomes and may

be considered a relative contraindication to pregnancy.

Cardiovascular disease is a leading cause of mortality for women with either type 1 or type 2 diabetes. A population-based study of acute myocardial infarction (AMI) during pregnancy shows that, although this condition is rare with a rate of 6.2 per 100,000 deliveries, AMI is associated with a mortality rate of 5.1%. In this study, diabetes was significantly associated with AMI[51]. The UK Obstetric Surveillance System (UKOSS) is currently collecting data on AMI in pregnancy (personal communication, UKOSS) and this may shed more light on risk factors, including diabetes. The presence of macrovascular complications should be considered during the preconception assessment for all women with longstanding type 1 diabetes and all women with type 2 diabetes. Screening with a minimum of an ECG should be arranged, and an exercise test should be considered if other risk factors are present, such as hypertension, hyperlipidemia, smoking, family history of premature cardiac disease and diabetic nephropathy.

Eating disorders associated with diabetes can present problems with glycemic control and may result in problems during pregnancy. The possibility of disordered eating patterns, including binge eating and insulin restriction to avoid weight gain should be considered during preconception assessments.

EFFECT OF PREGNANCY ON DIABETES

Hypoglycemia

Hypoglycemia, usually defined as blood glucose of less than 4 mmol/l, is a barrier to tight glycemic control. Women need to be aware that the tight control required before conception, and in pregnancy, may predispose them to more hypoglycemic episodes. Evers and colleagues demonstrated that the frequency of severe hypoglycemia is increased by two- to three-fold during the first trimester and is associated with a history of severe hypoglycemia, more than 10 years' duration of diabetes, HbA_{1C} below 6.6% and a higher total daily dose of insulin[52]. Factors related to pregnancy that contribute to hypoglycemia include nausea, vomiting and glucose transfer across the placenta to the fetus. The risk of hypoglycemia is increased particularly between meals and overnight when the woman is fasted. This risk is in addition to the peak of action associated with the use of isophane insulin, thus making between meal and before bed snacks important. Appropriate education with a diabetes specialist nurse and dietitian is extremely helpful not only for achieving optimal glycemic control preconception, but also in preparation for the early weeks of pregnancy. Information about balancing exercise with good glycemic control should be included during this education.

Due to the increased frequency of hypoglycemia, it is vital that appropriate treatment of hypoglycemia be discussed during preconception assessments. Prompt return to normoglycemia, after hypoglycemia, may help to reduce further blunting of the counter-regulatory responses. Animal data suggest an association between hypoglycemia and congenital malformations, but this has not been confirmed in human studies[53]. It is not known if the increased rate of congenital malformations seen in women with an HbA_{1C} between 5.6 and 6.8% is due to hypoglycemia or the effects of episodes of hyperglycemia, including those that result as a rebound effect of hypoglycemia treatment[10].

First-line hypoglycemia treatment should be consumption of fast-acting carbohydrates such as glucose tablets or a sugar containing drink. Once blood glucose levels have recovered, further hypoglycemia should be avoided by consumption of longer-acting carbohydrates such as a cereal bar, fruit, biscuits or the next meal if it is due. In addition, all women on insulin should have a supply of concentrated glucose

gel (Glucogel™, a 40% dextrose gel, is commonly prescribed in the UK) and a glucagon kit[8]. As emphasized by the American College of Obstetricians and Gynecologists (ACOG) family members and, if necessary, co-workers should also be educated in the recognition and treatment of hypoglycemia[54].

Changing insulin requirements

Insulin requirements change during pregnancy with a general increase as pregnancy progresses, although this effect varies between individuals. There appears to be a triphasic pattern of insulin requirements, which remain steady in the first trimester and increase thereafter[55]. Due to insulin resistance, women with type 2 diabetes require higher doses of insulin and experience greater increases in dosage than those with type 1 diabetes. Interestingly, in a prospective study of women with type 1 diabetes, after initial increases in insulin doses a fall in insulin requirements was observed between 7 and 15 weeks' gestation[56]. These changes, in combination with the need to balance near normal glycemic control with avoidance of hypoglycemia, result in the need for intensive blood glucose monitoring throughout pregnancy.

Diabetic ketoacidosis

During pregnancy women with diabetes are more susceptible to diabetic ketoacidosis (DKA). Kamalakannan and associates reviewed contributing factors such as increased insulin resistance and pregnancy induced lipolysis, along with precipitating factors for DKA which include infection, vomiting and poor compliance[57]. Prompt diagnosis and treatment of DKA is important in pregnancy because of the potential for fetal harm. DKA often develops quickly and may be associated with less marked hyperglycemia than is usual outside of pregnancy[58]. Despite this, episodes of DKA during pregnancy are fortunately rare due to intensive monitoring and tight blood glucose control. The preconception assessment provides an opportunity to ensure that all women with type 1 diabetes have a method of checking for ketones (either via urinary stick testing or with a meter with the appropriate ketone testing strips) and should check for them if blood glucose is raised above 12 mmol/l, especially if they should feel unwell with nausea, vomiting or abdominal pain. Women should be clearly informed that if they have high blood sugar levels with ketones, or evidence of urinary ketones with even moderate blood sugar elevations, they should seek medical help urgently rather than attempting to manage the situation themselves.

BREASTFEEDING

Many women with diabetes are not aware that there is no reason why they should not breastfeed, and breastfeeding should be encouraged, in the interests of both the mother and her baby. These facts should be presented at the preconception appointment and stressed throughout antenatal care appointments. It must be appreciated, however, that breastfeeding requires an increase in calorie intake accompanied by a decrease in insulin. Accordingly, breastfeeding diabetic women should be advised to have food before or during feeding[8]. Women with type 2 diabetes should also be aware that they can continue taking metformin or glibencamide whilst breastfeeding, because there is adequate information on the safety of the low levels of metformin and on the absence of glibencamide in breast milk[8,59,60]. As data on the safety of breastfeeding with the other oral hypoglycemic agents are limited, NICE recommends that they be avoided. In practice this means that type 2 diabetics treated with these agents before pregnancy are usually advised to stay on insulin until they have finished breastfeeding[8]. If women are taking other drugs, these too must also be considered in respect of breastfeeding.

EFFECT OF DIABETES ON PREGNANCY

Poor diabetic control has a significant adverse effect on pregnancy and is associated with an increased risk of untoward pregnancy outcomes. These possibilities should be discussed at the preconception appointment, not least because many of these effects can be modified by improving diabetic control before conception and maintaining good control throughout the pregnancy. Unfortunately both miscarriage and fetal anomalies are much more common in women with diabetes, with higher rates for both in women with poor pre-pregnancy control as reflected by the HbA_{1C} in early pregnancy (see above). However, it must be recognized, and explained to women that both miscarriage and fetal anomalies are not exclusive to pregnancies in diabetics, or those with poor control.

A comparison of miscarriage rates in 386 type 1 diabetics and 432 non-diabetic women reported a 16% miscarriage rate in both groups[61]. However, this simplistic assessment is misleading because, while there was no relationship between the miscarriage rate and HbA_{1C} level within the normal HbA_{1C} range, in the above normal range the miscarriage rates increased in an approximately linear fashion in parallel with increasing levels of HbA_{1C}. In a smaller study of 83 type 1 and type 2 diabetics, 95% of the miscarriages occurred in women with an HbA_{1C} level of more than 11.5%[62].

Suhonen and colleagues adjusted for factors including maternal age, duration of diabetes, parity and smoking, and found a relative risk for fetal malformations of only 1.6 for women with type 1 diabetes with an HbA_{1C} less than 5.6%[10]. Similarly, a comparison of type 1 diabetics with an early pregnancy HbA_{1C} above or below 7.5% demonstrated a nine-fold increase in the rate of congenital anomalies in the group with the higher HbA_{1C}[11]. The rate of fetal malformations increases even further with very high HbA_{1C} levels[13].

Because the very high rates of adverse pregnancy outcome can be improved with improved diabetic control before conception, it is absolutely essential that women with diabetes are aware of these risks before conception. They should also be provided with help to improve their control well before their first appointment in the antenatal clinic, as each 1% decrease in preconception HbA_{1C} halves the rate of adverse pregnancy outcomes[7].

Women with long-term diabetes are at greater risk of developing pre-eclampsia than the background population, and this risk is greater the longer the duration of the woman's diabetes, with a higher risk in women with pre-existing diabetic renal disease or hypertension[34,35]. Unfortunately, since both proteinuria and hypertension are common in pregnancies with long-term diabetes, it can be difficult differentiating between this phenomenon and developing pre-eclampsia. Unfortunately, these complications cannot be prevented by good glycemic control in pregnancy. Regardless, there are advantages in discussing these risks at the preconception appointment so that women are aware of potential problems and so that prophylactic treatment, i.e. low-dose aspirin (see above), can be considered and potentially started early.

Women are often aware of the risk of fetal macrosomia, leading to the birth of the classic cherubic infants of diabetics. However, they are often unaware that the risk of macrosomia (and related polyhydramnios) can be modified by good blood sugar control during the pregnancy, especially in the third trimester. The preconception appointment is an ideal time to discuss this effect of diabetes, and how it may be managed (see above). Fetal growth restriction can also complicate the pregnancies of women with diabetes and can have even greater implications for fetal outcome[6].

The CEMACH enquiry[1] showed that antenatal evidence of fetal growth restriction was associated with poor pregnancy outcome (OR 2.9, 95% CI 1.4–6.3, adjusted for maternal age and deprivation), whereas antenatal evidence of fetal macrosomia was not. Women should be reassured that fetal growth and amniotic fluid volume will be regularly assessed with serial ultrasound scans throughout pregnancy, and that decisions on pregnancy management will be directed by the scan findings. NICE recommends ultrasound scans every 4 weeks from 28 weeks' gestation[8], whereas the Australasian Diabetes in Pregnancy Society only recommends growth scans at 28–30 weeks' and 34–36 weeks' gestation[63].

Since there is increased risk of fetal and maternal trauma during delivery with macrosomia, the risks and benefits of attempting vaginal birth (possibly with induction of labor) or delivery by planned cesarean section need to be considered if macrosomia is diagnosed by ultrasound scan[8]. The CEMACH enquiry[1] reported shoulder dystocia in 7.9% of vaginal births in diabetic women, with no difference between type 1 and type 2 diabetics; but a 42.9% incidence of shoulder dystocia was reported when the baby weighed 4.5 kg, or more[6]. Despite this, it must be acknowledged that it is not possible to accurately determine fetal weight before delivery and that a significant error (8–15%) exists in fetal weight estimation by ultrasound[63]. Unfortunately, accuracy of estimated fetal weight is worse in women with diabetes and when the fetus is macrosomic[65,66]. Neither shoulder dystocia nor the possible sequelae for the fetus (Erbs palsy) can always be prevented, but awareness of the possibility and proper and timely management of the dystocia if it occurs is likely to decrease the risk of long-term complications in the baby[67]. Because of this, every maternity unit should have guidelines for the management of shoulder dystocia and should have regular drills for all labor ward staff in its management. Since the majority of macrosomic babies do not experience shoulder dystocia, the Royal College of Obstetricians and Gynaecologists (RCOG) in the UK does not recommend delivery by cesarean section with suspected macrosomia in non-diabetic women, but does recommend consideration of planned cesarean section in diabetic women because of the relatively high rates of shoulder dystocia[67]. This recommendation is endorsed by both ACOG and NICE[8,54,68].

Induction of labor does not decrease the maternal or neonatal morbidity of shoulder dystocia but does decrease the risk of a large for gestational age (LGA) baby and the incidence of shoulder dystocia. Therefore, ACOG expressly advises against induction of labor for suspected fetal macrosomia[54]. A randomized controlled trial of 200 women with insulin-requiring diabetes (mainly gestational diabetes) and a case–controlled study of 260 diabetics both compared induction of labor at more than 38 weeks' gestation with expectant management[69,70]. Both studies found an increase in the rates of LGA babies and shoulder dystocia in the expectant management group, with no increase in cesarean section rates in the induction group. NICE therefore recommends induction of labor after 38 completed weeks in diabetics[8]; this differs from the advice of the Australasian Diabetes in Pregnancy Society which is that induction of labor should 'only be considered for obstetric and/or fetal indications'[62].

Unheralded intrauterine death remains a significant contributor to perinatal mortality in pregnancies complicated by diabetes mellitus. Unfortunately, conventional tests of fetal well-being are poor at predicting these events[8]. The CEMACH investigation of current (2002/2003) UK management of pregnancy in diabetics reported a stillbirth rate of 26.8 per 1000 births (95% CI 19.8–33.8 adjusted for maternal age), with 27.6% of these stillbirths occurring after 37 weeks[1]. Women may be aware of this statistic before they conceive and need to be reassured that the rate is fairly low

in women with well controlled diabetes. It has long been common practice to advise women with diabetes that delivery should occur early because of the risk of unexpected stillbirth; as noted above, NICE advise delivery after 38 completed weeks[8].

The 2005 CEMACH report[1] on 3808 pregnancies in women with diabetes in 2002/2003 showed that women with diabetes have fairly high rates of induction of labor (39%) and cesarean section (67%). Ideally women will be aware of these data before they conceive, but it is equally important that they are aware that neither is inevitable! In the UK the rate of induction of labor is of course higher in this group of women, as it is advised that even with well controlled diabetes delivery should be considered after 38 weeks (see above)[8]. Although the 2005 CEMACH report showed a UK cesarean section rate of 67% in women with diabetes compared to 24% in the non-diabetic population[1], this high rate is not inevitable as shown by the cesarean section rate at our hospital in women with pre-existing diabetes (40% in 2006 and 42% in 2007).

EFFECT OF DIABETES ON THE NEONATE

Even before conception women worry about the effect their diabetes may have on the newborn baby. It is thus appropriate to briefly discuss neonatal management during preconception counseling. In particular, women should be reassured that, although the babies of diabetic women require careful monitoring and should therefore be delivered in a unit with appropriate neonatal facilities, many newborns experience no serious problems and stay with their mothers in the neonatal period, as recommended by NICE[8].

Diabetes of all types is a recognized risk factor for neonatal hypoglycemia, and, though less likely, can still occur in the babies of mothers with well controlled diabetes. In a study on the frequency, risk factors and long-term effects of neonatal hypoglycemia, 9.18% of the 1023 babies admitted to the neonatal unit were hypoglycemic; of these, 34.1% were born to diabetic mothers[71]. An audit from the National Women's Hospital, New Zealand, showed that of the 136 babies of diabetic mothers admitted to the neonatal unit the indication for admission was hypoglycemia in 51% of cases[72]. Another study compared 78 women with rigorously controlled diabetes and 78 controls; these authors noted neonatal hypoglycemia in 14% of the neonates of diabetic mothers compared to 1% of the controls[73]. As monitoring for and good management of hypoglycemia is very important, every maternity unit should have written guidelines for blood sugar management of the neonates of diabetic women[8]. Women require reassurance that good control can often prevent neonatal hypoglycemia, and that early feeding (preferably breastfeeding), followed by feeding at frequent intervals, will help the baby maintain its blood glucose levels[8]. Neonatal blood glucose testing, preferably after feeding, routinely should be carried out 2–4 hours after birth. Ideally babies of women with diabetes should be kept with their mothers, and every attempt should be made to control the babies' blood sugar without resort to parenteral glucose (which would require admission to the neonatal unit), though this should obviously be considered if the babies blood glucose level does not improve with less invasive measures[8].

Polycythemia, hyperbilirubinemia, hypomagnesemia, previously unrecognized congenital heart disease and cardiomyopathy are all more common in the babies of women with diabetes, but all are rare, especially if the diabetes is well controlled in pregnancy and the baby is delivered at or near term. Screening should therefore only be recommended in babies with clinical signs[8]. So that the babies of diabetic mothers can be monitored for rare neonatal complications, and to ensure that the baby is maintaining its blood glucose levels

and has established a good feeding pattern, transfer to community care should not occur before the baby is 24 hours old[8].

RISKS OF INHERITING DIABETES

The risk of the child inheriting diabetes is a frequently asked question. For parents with type 1 diabetes this risk is higher for children of diabetic men (6%) than women (1.3%); for parents with type 2 diabetes, the risk is 15% for one first-degree relative rising to greater than 60% if both parents have type 2 diabetes[74]. Interestingly, there is a higher risk for developing type 2 diabetes if the mother is affected compared to the father, suggesting that the intrauterine environment may be a predisposing factor and possibly indicating that there could be benefits of intensive glucose control that extend beyond pregnancy[75].

SUMMARY

Optimal management of diabetes mellitus is important throughout pregnancy and ideally starts prior to even starting attempts to conceive. The evidence above demonstrates how essential this is to improve each woman's chance of a good pregnancy outcome.

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6

Prolactinomas, hypothyroidism, hyperthyroidism and pregnancy

Alper Gürlek and John A. H. Wass

PROLACTINOMAS

By definition, prolactinomas are prolactin (PRL)-secreting tumors of the pituitary which are almost invariably benign in nature. They are the most common form of pituitary tumor. Although microprolactinomas (diameter <1 cm) may be easily manageable by dopamine agonists, macroprolactinomas (diameter >10 mm) may be challenging in this respect because of compression and invasion of the surrounding vital structures, recurrence after surgery and resistance to medical treatment[1, 2].

Prolactinomas are more common in women than in men with a peak incidence in childbearing age[1]. It is, therefore, not unexpected that women with prolactinomas may either desire to become pregnant or find themselves pregnant with the tumor *in situ*.

Effect of pregnancy on prolactinoma growth

As gestation advances, estrogen-induced stimulation of PRL synthesis by lactotrophs causes an increase in PRL levels which reach a peak value of 150 ng/ml at term[3]. Prolactinomas tend to enlarge during pregnancy principally by two mechanisms: (1) loss of shrinkage effects of dopamine agonists after their withdrawal upon diagnosis of pregnancy; and (2) induction of tumor growth by estrogen secreted from the placenta[4].

Previous observations regarding prolactinoma growth during pregnancy have provided inconsistent results in terms of micro- and macroprolactinoma growth, with microprolactinoma risk of progression in size being lower than that of a macroprolactinoma. For example, only 11 out of 246 women with a microprolactinoma displayed asymptomatic tumor progression during pregnancy, and none necessitated surgical intervention owing to tumor growth[5]. Symptomatic enlargement of macroprolactiomas, on the other hand, reached 31% in a pooled analysis of patients from three different series of pregnant patients[5–7]. A surgical approach was required in 8.5% of these patients. Macroprolactinomas which have undergone surgical excision or irradiation before gestation also have a low tendency for further growth (5%), a feature which is comparable with microprolactinomas. Under such circumstances, it may be advisable for a patient with a macroprolactinoma to be operated or irradiated before planning of pregnancy.

Effect of dopamine agonists on fetal growth and development

A major concern regarding the management of a prolactinoma during pregnancy is the safety of use of dopamine agonist drugs. As mentioned

above, dopamine agonists are the drugs that are used to control the secretion and size of prolactinomas, as well as being effective in the achievement of fertility. Because fertility restoration is highly likely (90%) with use of such agents, most women have been exposed for 2–3 weeks when the diagnosis of pregnancy is eventually made. This issue makes the safety of these agents extremely important. As some prolactinomas grow during pregnancy, it would be advantageous to shrink the tumors by use of dopamine agonists which also would lead to alleviation of the compressive symptoms without the need for surgery.

The dopamine agonist drug bromocriptine has long been used in the medical treatment of prolactinomas, and much experience regarding its safe use during pregnancy exists. Krupp and Monka reported the results of a 4-month to 9-year follow-up of 988 children exposed *in utero* to bromocriptine, and concluded that the drug has no negative effect on physical development[8]. The incidence of spontaneous abortions, ectopic pregnancies and congenital malformations in pregnancies during which bromocriptine was used was comparable with that of the normal population[8]. Although discontinuation of this drug has long been advised when pregnancy is diagnosed, rapid elevations in prolactin and progression in tumor growth during the first trimester may be observed upon withdrawal[9]. Such progression may be unresponsive to bromocriptine reinstitution, and newer compounds like cabergoline may be required for treatment. Cabergoline is currently the most frequently used agent in prolactinoma treatment because of its greater tolerability and efficiency compared with bromocriptine[10]. Experience regarding its use in pregnant women with prolactinoma is, however, limited. In experimental models of pregnancy, cabergoline was not found to be teratogenic[11]. Analyses of cabergoline-induced gestations in humans revealed no increases in pregnancy-associated problems such as miscarriage and fetal malformations[12]. It is worth noting that cabergoline has a long duration of action keeping prolactin levels suppressed up to 4 months after its withdrawal[13]. The Pituitary Society therefore advocates withdrawal of cabergoline upon a missed menstrual cycle in patients with prolactinoma to make sure that the fetus does not become exposed during the critical first trimester[14].

Fewer, albeit more discouraging, data exist regarding the safe use of pergolide in pregnancy. Two major and three minor congenital malformations have been reported in 38 pregnancies of women taking pergolide[15]. Pergolide is associated with increased risk of spontaneous abortions, minor congenital malformations and intentional abortions, precluding its safe use in pregnant women[4]. As a result, it is not wise to recommend pergolide for restoring fertility in patients with prolactinoma who desire pregnancy.

Quinagolide is also available for the medical management of prolactinoma. Similar to pergolide, its use also seems to be unsafe in pregnancy. In a review of 176 pregnancies during which quinagolide had been used for a median of 37 days, fetal outcomes were poor. Spontaneous abortion was reported in 24 cases, ectopic pregnancy in one, and stillbirth at the 31st week of gestation in an additional case[16]. Moreover, severe fetal malformations including spina bifida, cleft lip and Down syndrome were noted in the group who survived[16]. Under such circumstances, quinagolide therapy should not be instituted in women with a desire for pregnancy.

Recommendations for the treatment of prolactinomas in pregnancy

Microprolactinomas

No clinical trials have compared the outcomes of women with microprolactinomas who have been treated with dopamine agonists during pregnancy with those who have not, and some experts choose to continue these agents during pregnancy. Nonetheless, a general sense exists toward discontinuation of dopamine agonists upon conception. The patient should then be informed about a small risk of tumor enlargement induced by pregnancy-associated hormonal changes. The patient must also be clearly and repeatedly informed that she should immediately notify her physician if any change in visual acuity or a defect in visual field should occur. Perimetric evaluation should occur on a bimonthly basis[17]. If the patient remains symptom free (no headache, no visual field problem), no intervention is required. After parturition, the patient may resume dopamine agonists if she does not intend to breastfeed. If, on the other hand, she wishes to do so, a magnetic resonance imaging (MRI) of the pituitary should be obtained to ensure there has been no progression in tumor size.

Conversely, the patient may have developed signs and symptoms suggestive of tumor progression as exemplified by new-onset headaches or visual field defects. In such instances, urgent pituitary imaging, preferably by MRI, is appropriate. It should be noted that PRL levels do not always rise in pregnant women with microprolactinomas as is the case in the nonpregnant women. PRL levels rise over the first 6–10 weeks after drug withdrawal and do not usually increase further after that period[9].

Since PRL rise does not accompany tumor growth[18], routine follow-up of PRL levels is not helpful as a means to detect changes in tumor size. In the event the tumor grows, the patient may be treated with dopamine agonists in an attempt to reduce the size. If this therapy is insufficient, transsphenoidal tumor removal (preferably in the second trimester), or early delivery in the third trimester may be proposed[4]. Figure 1 provides an algorithm for the management of microprolactinomas.

Macroprolactinomas

Treatment for pre-pregnant or pregnant women with macroprolactinomas is much more complex, being primarily based on the extent and size of the tumor. Since macroprolactinomas tend to be invasive, pregestational evaluation is crucial. If the tumor is restricted to the sellar region or shows a small infrasellar extension, then dopamine agonists may be used alone[4].

Patients with macroadenomas having undergone treatment with dopamine agonists should strongly be advised not to become pregnant until it is demonstrated that a significant shrinkage of the tumor within the sellar cavity has been achieved. Then the patient may more safely attempt pregnancy. After discussing the risk of progression with the patient, abortion may be considered as an option for large tumors showing no shrinkage with dopamine agonists. The responsive tumors in which there has been sufficient shrinkage may be handled in accordance with the principles mentioned above for microprolactinomas[4]. If abortion has been induced in an unresponsive patient, future pregnancy may be planned after debulking surgery is performed.

Macroprolactinomas with suprasellar extensions pose a serious risk of tumor enlargement with resultant chiasmal compression and other problems if dopamine agonists are used as sole therapy. In such instances, the most conservative approach would be to perform transsphenoidal surgery for tumor debulking. Afterwards, dopamine agonists must be reinstituted to normalize PRL levels which may interfere with ovulation. Since radiotherapy is considered harmful by increasing the risk of hypopituitarism, it is not generally recommended in an attempt to control tumor growth. Another option in such cases may be continuation of the dopamine agonist treatment throughout the gestational period[19]. Such an approach does not seem to pose a significant risk to fetal outcome[20]. If a woman

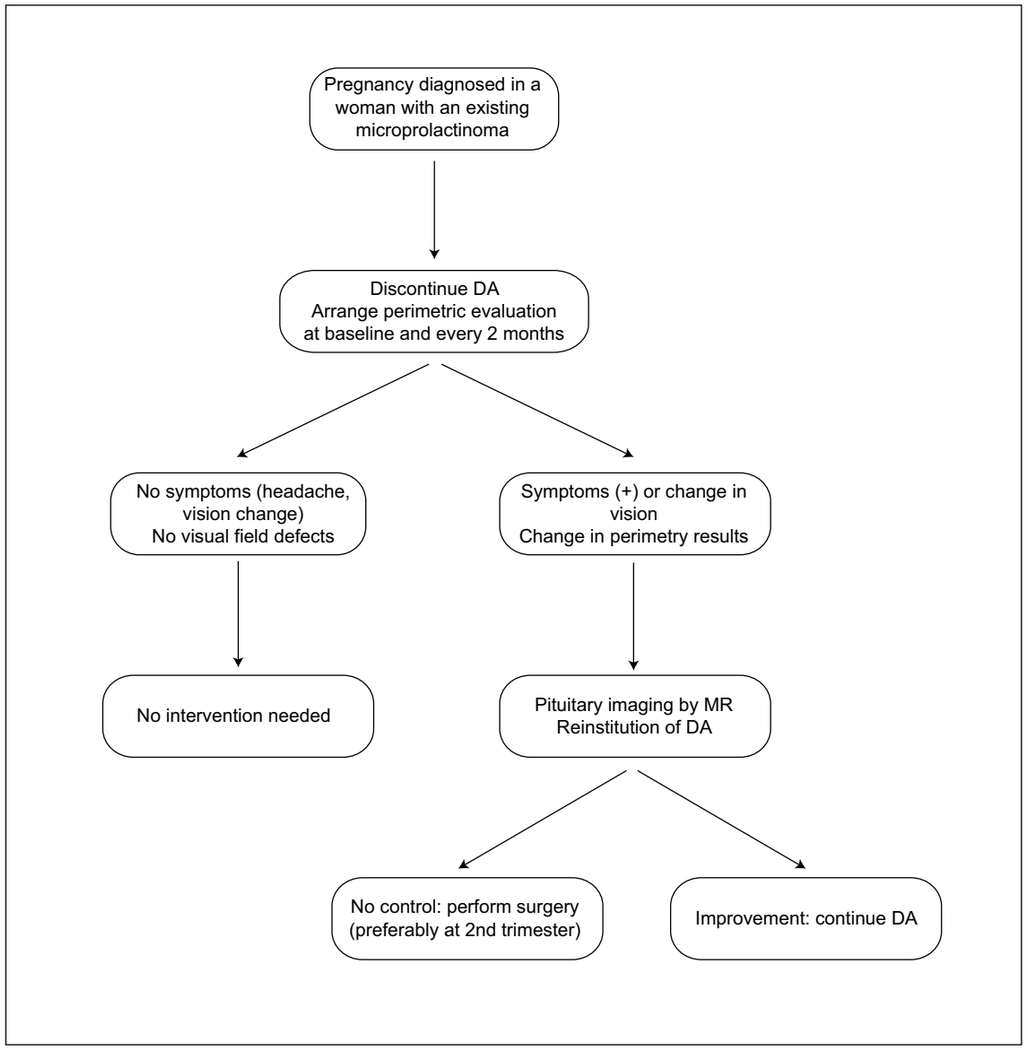

Figure 1 Management algorithm for microprolactinomas in pregnancy. Adapted from references 1 and 17. DA, dopamine agonist; MR,magnetic resonance

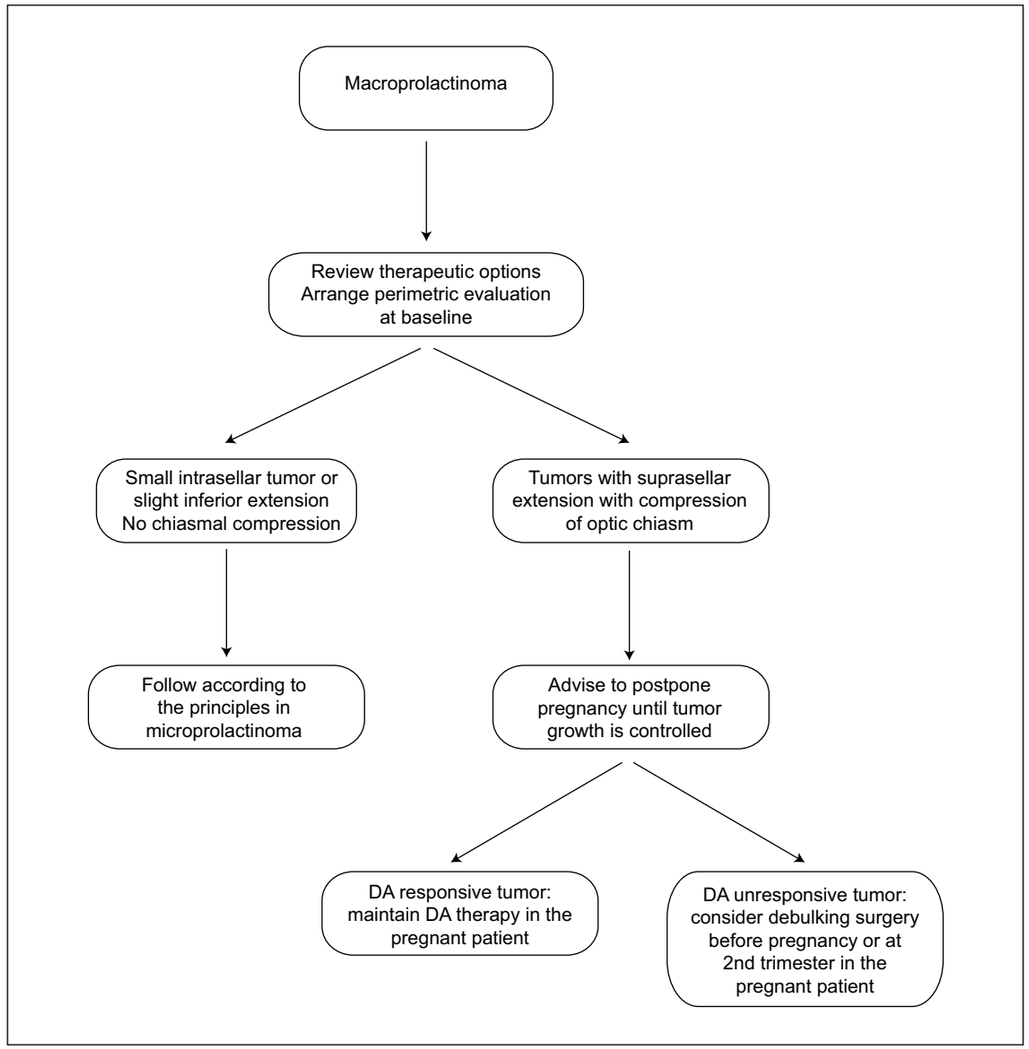

Figure 2 Management algorithm for macroprolactinomas. Adapted from references 1 and 17. DA, dopamine agonist

presents with a history of inadvertent dopamine agonist use in late pregnancy, therapeutic abortion should not be considered unless a fetal abnormality is present. In such cases, discontinuation of the drug and normal delivery may be recommended. Since any type of surgical procedure is accompanied by at least a 1.5–5-fold risk of fetal loss during pregnancy[21], the best initial approach in a patient with enlarged tumor would be initiation of medical therapy. Surgery should be reserved for failure of this conservative approach as exemplified by deterioration of visual field defects or no effect of dopamine agonists on tumor size. Figure 2 presents an algorithm for the management of macroprolactinomas.

HYPOTHYROIDISM

After diabetes, thyroid disease is the second most common disorder affecting women of reproductive age. Pregnancy alters the clinical presentation of thyroid diseases, and also modifies thyroid function tests[22]. In normal pregnancies, a fall in thyroid-stimulating hormone (TSH) concentrations and increase in serum free thyroxine (T4) concentrations occur during early weeks. This effect is primarily mediated by the TSH-like activity of placental-derived human chorionic gonadotropin[23]. Conversely, in the late stages of pregnancy, a significant decrease is observed in free T4 levels[23]. These physiological changes may

challenge the interpretation of thyroid function tests in hypothyroid and hyperthyroid pregnant women. For example, hypothyroidism may be masked by the aforementioned changes in free T4 and TSH levels in early pregnancy.

The prevalence of autoimmune thyroiditis in Western developed countries in women of childbearing age ranges between 5 and 15%[24]. The prevalence of overt and subclinical hypothyroidism in this same age group is 0.3–0.5% and 2–3%, respectively[24], with similar values during pregnancy[25]. The main cause of hypothyroidism during pregnancy is autoimmune thyroiditis, particularly in iodine-sufficient areas[26]. In underdeveloped parts of the world, however, the commonest cause is iodine deficiency[26]. Severe iodine deficiency causes endemic cretinism characterized by mental and motor retardation, and deafness[23]. Other less common causes include radioiodine ablation and surgical removal of the thyroid gland[23]. Iron compounds are commonly used in pregnant women, and their interference with intestinal T4 absorption may also worsen hypothyroidism during pregnancy[23]. To avoid this problem, iron compounds should be given at least 4 hours after T4 has been administered 1 hour before breakfast.

The impact of pregnancy on hypothyroidism

Patients with autoimmune thyroiditis are prone to developing subclinical or clinical hypothyroidism with advancing gestation. This occurs primarily due to a lack of capability on the part of the affected thyroid gland to increase its secretory reserve to overcome the increased thyroid hormone demands. Subclinical hypothyroidism also tends to evolve into clinically overt disease by the same mechanism[27].

The impact of hypothyroid state on pregnancy and its outcome

Autoimmune thyroid disease is more common in infertile compared with fertile women[28,29]. Although hypothyroidism may be implicated in infertility, thyroid autoimmunity *per se* is not associated with impaired fetal implantation[28,29]. The success rate of *in vitro* fertilization procedures is lower in patients with untreated hypothyroidism, but not in those with autoimmune thyroiditis and normal thyroid function[28,29]. It is reasonable to advocate appropriate treatment of hypothyroidism and normalization of thyroid function in women with a desire for pregnancy. This process is also valid for patients who cannot spontaneously conceive and require assisted fertilization. How often this occurs in IVF clinics worldwide is unknown.

Obstetric complications associated with subclinical and overt hypothyroidism include miscarriage, anemia, pre-eclampsia, placental abruption and preterm delivery[30,31]. The incidence of postpartum hemorrhage and risk of newborn acute respiratory distress syndrome is also increased in untreated hypothyroidism[30]. In a prospective randomized trial, early intervention with thyroid hormones at 5–10 weeks after conception significantly reduced the risk for miscarriage and preterm delivery compared with untreated control subjects[32]. These results underline the importance of early treatment of hypothyroid patients when pregnancy is diagnosed.

Apart from the aforementioned obstetric complications, untreated hypothyroidism may also be implicated in impaired fetal neurodevelopment, particularly when hypothyroidism is present in early pregnancy[27]. Even mild deficiencies may be associated with reduced cognitive and intellectual function in the offspring[33]. The fact that neural developmental

defects are related with the duration and severity of the hypothyroidism supports the need for the patient to begin thyroxine replacement immediately upon detection of hypothyroidism. Even isolated hypothyroxinemia without concomitant TSH elevation in the early gestational period may lead to a lower psychodevelopmental index in the newborn[34]. Fortunately, most newborns recover spontaneously and there is insufficient evidence to advocate treatment of this condition in newborns[34]. An important issue to be addressed is whether therapeutic abortion should be induced in a pregnant woman during late pregnancy whose severe hypothyroidism has previously remained undiscovered and untreated. The appropriate approach at this stage is debatable, and most obstetricians would hesitate to terminate the pregnancy. Whatever is decided, parents should be carefully notified about the potential brain damage caused by prolonged hypothyroidism.

Treatment of hypothyroidism

Before conception, patients with known hypothyroidism should be assessed for TSH level. The TSH value should be less than 2.5 mU/l[35,36]. In patients with euthyroid autoimmune disease, this TSH cut-off may also be used, although there is no direct evidence in favor of this approach[27]. Once pregnant, the patient should be advised to increase her thyroxine dose by at least 30% to avoid inadequate fetal thyroid hormone delivery during the critical period of organogenesis and brain development[37]. The amount of this increase may also be based on the underlying cause of hypothyroidism. Patients with Hashimoto's thyroiditis require less dose augmentation than do those who have undergone surgical or radio-ablation of the thyroid gland[38].

As patients may be diagnosed initially during pregnancy, routine assessment of thyroid function at the first antenatal visit seems mandatory to not overlook the condition. As stated above, the TSH level should be normalized as quickly as possible by giving more than daily maintenance doses. The patient should be seen after 4–5 weeks of treatment, and on a 6-weekly basis thereafter. Dose titration should assist in achieving target TSH levels (<2.5 mU/l at first trimester and <3 mU/l thereafter). A wide range of thyroxine doses may be required to achieve this goal (25–325 μg/day)[39]. After parturition, doses can be reduced for most women over a few weeks[39]. The thyroid status should be closely monitored as autoimmune thyroiditis increases the risk of development of postpartum thyroiditis.

HYPERTHYROIDISM

The prevalence of hyperthyroidism in pregnancies is 0.2%[23]. As many of the typical symptoms of hyperthyroidism (nervousness, tremors, tachycardia, weight loss, excessive sweating) are also compatible with the normal physiological changes of pregnancy, identification of patients with new-onset hyperthyroidism may be problematic. As noted above, pregnancy is associated with changes in thyroid function tests, so that free T4 levels and free T4 index are normally elevated and TSH level is depressed in early pregnancy. Since resin triiodothyronine (T3) uptake is normally decreased in pregnant women, its increase may indicate the presence of underlying hyperthyroidism.

As is the case in the non-gestational period, Graves' disease is the most common cause of thyrotoxicosis during pregnancy. The autoantibodies directed against TSH receptors have the ability to cross the placental barrier and bind to fetal follicular epithelial cells. The result is neonatal Graves' disease causing hyperthyroidism and thyroid enlargement. Apart from Graves' disease, gestational trophoblastic disease, toxic multinodular or uninodular goiter, viral thyroiditis and pituitary TSH-secreting

tumor may also cause hyperthyroidism during pregnancy[23].

Impact of hyperthyroidism on pregnancy outcome

The importance of timely diagnosis and treatment of hyperthyroidism complicating pregnancy is related to its association with seriously adverse pregnancy outcomes such as stillbirth, preterm delivery, pre-eclampsia and intrauterine growth retardation[40]. If present at conception, untreated hyperthyroidism may lead to spontaneous abortion. It is wise to bring the patient to euthyroid status before planning of pregnancy. Another important aspect of hyperthyroidism is that radionuclide studies should not be ordered in an attempt to make the differential diagnosis of thyrotoxicosis due to the risk of destruction of fetal thyroid epithelial cells[41].

Impact of pregnancy on the course of Graves' disease

Graves' disease generally improves in the second and third trimesters of pregnancy allowing reduction in the dosage and even discontinuation of antithyroid medication[42]. The disease may show reactivation during the postpartum period[42].

Treatment of hyperthyroidism

Women with Graves' disease may be treated by antithyroid drugs during pregnancy. For this purpose, propylthiouracil is superior to metimazole because of lower rates of transplacental passage. At high doses, however, both may pass the placenta and affect fetal thyroidal function[35,42]. Another advantage of propylthiouracil comes from its ability to block the conversion of T4 to T3 by inhibiting deiodinase. This helps to get a quicker and more pronounced suppression of thyrotoxicosis. A slightly elevated T4 level should be allowed to ensure that the fetus receives adequate amounts of thyroid hormones to avoid hypothyroidism[42]. Propylthiouracil may be given 100–150 mg t.i.d. initially; the patient then should be seen after 2–4 weeks for reassessment of thyroid function tests[23]. At that stage, the dosage may be titrated for maintenance. The beta blocker drug propranolol should be used with great caution to control adrenergic symptoms[23]. In the event that the symptoms are not adequately controlled in severe cases, thyroidectomy should be considered, preferably during the second trimester[23]. Radioiodine treatment is contraindicated due to risk of fetal thyroid destruction, and definite therapy should be postponed until after parturition[23].

CONCLUDING REMARKS

Women with microprolactinomas should receive preconceptional counseling to increase fertility by medical treatment with dopamine agonists. Current practice is to withdraw these agents upon diagnosis of pregnancy. It is preferable that macroadenomas be cured before conception, since they tend to grow during pregnancy causing significant visual problems. Patients with prolactinomas should consult with an endocrinologist and neurosurgeon for medical and surgical treatments, respectively. Since untreated hypothyroidism may decrease fertility, early detection is warranted and the patient should be treated and followed appropriately by an endocrinologist. Untreated hyperthyroidism at the time of conception is associated with increased risk of spontaneous abortion. To avoid this unwanted complication, it is mandatory that the patient consult with an endocrinologist in order to achieve a euthyroid state when pregnancy is planned.

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7

Autoimmune and connective tissue disorders

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Pregnant women with autoimmune rheumatic diseases, especially systemic lupus erythematosus (SLE) and systemic sclerosis, are at high risk of maternal disease flares, adverse fetal outcomes and potential drug teratogenic effects, making the management of these women particularly challenging. With improvements in diagnosis and treatment, however, these risks can be minimized by appropriate timing of pregnancy and optimization of therapy before conception.

Preconception counseling represents a unique opportunity to optimize pregnancy outcome in women with chronic medical illnesses, those with autoimmune rheumatic diseases being no exception. This chapter reviews the impact of these diseases and their therapies on the mother and her fetus, the effect of pregnancy on these disorders with special emphasis on issues that should be discussed with women before they attempt to become pregnant, and measures that might be undertaken to optimize pregnancy outcome. The information provided can be used to counsel anxious mothers preconceptionally on what to expect during pregnancy and how to increase the likelihood of a successful pregnancy and the birth of a healthy infant.

SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is the most common autoimmune disease affecting women during childbearing years, with a reported prevalence of 1 per 1000 women[1]. It is characterized by deposits of antigen–antibody complexes in capillaries and various visceral structures. Although once considered a contraindication to pregnancy, advances in disease management and perinatal monitoring now make pregnancy outcome in women with this multisystem, relapsing and remitting disease more favorable. Nonetheless, significant risk of morbidity to both the mother and fetus still may occur. No evidence suggests that SLE or any of the connective tissue disorders affect fertility, as ovarian failure is rare in these entities[2]. Prior treatment with alkylating agents such as cyclophosphamide is one of the risk factors for infertility; however, this risk is related to the total dose and the age of the patient at exposure[2–4]. Of interest, one population-based study has shown a smaller family size in women with SLE[5]. Ovulation induction appears to increase the risk of flare and thrombosis, especially in women with antiphospholipid (aPL) antibodies[6,7].

How does pregnancy affect SLE?

Pregnancy may exacerbate SLE activity[2,8] and increase the likelihood of maternal disease flares, which are reported to occur in 13.5–65% of pregnant women with SLE[8,9]. The most common SLE manifestations in pregnancy include constitutional symptoms and renal, skin and joint problems[8]. The risk of lupus flare during pregnancy is increased dramatically in women with active lupus in the

6 months prior to conception[2,10,11], whereas women in prolonged remission are less likely to experience an increase of lupus activity during pregnancy[12,13]. In a cohort of 267 pregnancies to women with SLE, the risk for significant SLE activity during pregnancy was significantly higher in women with disease activity shortly before conception (58% versus 8%; $p < 0.001$)[14]. Unfortunately, measuring lupus activity during pregnancy is not very straightforward, as some laboratory tests that are useful in non-pregnant women are less reliable during pregnancy[15]. Women with renal involvement are also at risk of deterioration in pregnancy, especially in the presence of hypertension, proteinuria (>1 g/24 h), glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 and high baseline serum creatinine level at the time of conception[16,17]. Renal flares during or after pregnancy are observed in up to one-third of cases[16], and irreversible renal impairment is reported in 0–10% of these[18,19]. Some severe cases, albeit rarely, evolve to maternal death secondary to end-stage renal or multisystem failure[20,21]. Nonetheless, a recent multicenter study on 113 pregnancies occurring in 81 women with pre-existing biopsy-proven lupus nephritis suggested that pregnancy can be successful in most instances, even for those with severe renal involvement at onset of pregnancy[16]. Hypocomplementemia was the best predictor of adverse fetal outcome, and therapy with low-dose aspirin was significantly associated with better fetal and neonatal survival. Although pulmonary hypertension is uncommon in lupus, it confers a high risk of maternal death when it occurs in pregnancy[22,23]. Women on dialysis or with renal transplants can achieve successful pregnancy but have higher maternal and fetal complication rates[24].

How does SLE affect pregnancy?

Pregnancy outcomes have improved dramatically over the past 40 years, with the pregnancy loss rate falling from 43% in the 1960s to 17% by 2003, approximating the pregnancy loss rate in the general population in the United States[25]. In addition to spontaneous miscarriage, SLE is associated with increased risks of intrauterine fetal death (5–16%)[14], pre-eclampsia (13–35%)[19,26–28], intrauterine growth restriction (IUGR) (9–23%)[14,28] and preterm delivery (30%)[2,22,25,27,28]. These complications are more common in women with lupus nephritis, aPL antibodies, hypertension and in those with active disease at the onset of pregnancy[2,29]. Women with severe renal impairment (serum creatinine over 2.8 mg/dl) have less than a 30% chance of having a successful pregnancy[24]. Of the aPL antibodies, lupus anticoagulant is the most strongly associated with recurrent fetal loss[30]. Among women with SLE, the prevalence of aPL antibodies ranges from 15 to 30% for anticardiolipin antibodies and from 15 to 34% for lupus anticoagulant[31–34]. In addition, aPL antibodies in women with renal involvement represent a strong risk factor for thrombotic events, fetal loss and a worse renal outcome in long-term follow-up[34]. During pregnancy women with SLE are at particular risk of maternal venous and arterial thrombotic events, especially in the first 6 weeks' postpartum, with a reported incidence of up to 1.7%[35]. Evidence shows that aPL antibodies may further increase the risk for vascular thrombosis in women with lupus[36]. Other risk factors include hypertension, smoking and immobility. Clowse and colleagues recently reviewed the Nationwide Inpatient Sample, a large database with detailed information on 20% of all hospitalizations in the United States[35]. This is the largest study to date of SLE during pregnancy, reviewing more than 16.7 million admissions for childbirth over 4 years. Of these, 13,555 were to women with SLE. These investigators found an alarming 20-fold increased risk of maternal mortality in women with SLE (325 per 100,000 live births). In addition, the study confirmed previous reports of increased risks

of thrombosis, infection, thrombocytopenia, transfusion, preterm labor and pre-eclampsia. Morevoer, women with SLE also had a higher rate of cesarean delivery (36.6% versus 25.0%; OR 1.7, 95% CI 1.6–1.9), a finding in agreement with previous studies[26,37].

Neonates of mothers with the anti-Ro and anti-La antibodies may be affected by transplacental passage of these antibodies. This can range from cutaneous neonatal lupus – the most common manifestation of neonatal lupus observed in newborns of up to 4% of women with these antibodies[38] – to the most serious manifestation, i.e. congenital heart block. Although rare – affecting 2% of neonates of mothers with these antibodies[38,39] – this condition may be more common in women with hypothyroidism[40] and can result in intrauterine fetal death. It entails significant morbidity and even mortality, with almost all affected infants requiring pacemakers and a cumulative probability of survival at 3 years of age of 80%[41]. On the other hand, in the absence of active disease, hypertension, renal involvement, or aPL antibodies, women with SLE have a complication rate that approaches that of the general population[25,29].

Preconception counseling

Ideally, the management of pregnancy in SLE should be undertaken by a multidisciplinary team starting before conception and continuing throughout pregnancy in order to ensure the best obstetric outcome. The team should include but not be limited to a rheumatologist/internist, a maternal fetal medicine specialist with experience in management of women with SLE, and a nephrologist, depending on the woman's renal status. A preconceptional counseling visit is important to estimate the woman's risk profile, to discuss the potential complications and to establish an appropriate management plan.

SLE is not a contraindication to pregnancy with the exception of conditions that are associated with high maternal mortality rates, including pulmonary hypertension and renal failure[2,35,42]. For example, in women with symptomatic pulmonary hypertension, the risk of maternal mortality is estimated to be higher than 30%[43]. That having been said, the risk of complications during pregnancy is not uniform in all women with SLE. Women with active disease within the last 6 months prior to conception should be advised to avoid pregnancy[1,2,10,19,24] because this has been associated with an increased risk of lupus flare and poor pregnancy outcome.

Because women with SLE frequently require treatment throughout pregnancy, a thorough review of current medications is essential during the preconception visit[44]. Women should be instructed to avoid FDA pregnancy category X medications as well as most category D medications unless potential maternal benefits outweigh fetal risks.

Drugs that can be continued during pregnancy include prednisolone, azathioprine, cyclosporin A and hydroxychloroquine[2]. Corticosteroids have been used extensively and safely in patients with SLE during pregnancy. Azathioprine use in pregnancy is not associated with a significant increase in fetal abnormalities[45]. Most experts advise continuation of hydroxychloroquine in women contemplating pregnancy, as this medication decreases the risk of flares and improves the prognosis of SLE nephritis[2,45,46]. In fact, its withdrawal is frequently associated with subsequent flares in pregnancy[2,47,48] and the need for higher doses of corticosteroid therapy. In addition, hydroxychloroquine has a very favorable safety profile with no increased risk of fetal malformations identified in several hundred pregnancies exposed to it during the first trimester[45,47,49]. Methotrexate, mycophenolate mofetil (MMF) and cyclophosphamide are teratogenic and thus are contraindicated in pregnancy. MMF use during pregnancy is associated with an

increased risk of first trimester pregnancy loss and congenital malformations including those of the external ear and other facial malformations such as cleft palate and lip[50]. Cyclophosphamide is associated with a 16–22% risk of congenital malformations after first trimester exposure[45]. Women on any of these medications should be switched to safer alternatives such as azathioprine, as sudden withdrawal may precipitate a flare during pregnancy. Whereas some authorities recommend discontinuation of these medications at least 3 months prior to conception[2], others suggest a 6-month interval for stabilization of any preconception drug changes[51].

Traditional non-steroidal anti-inflammatory drugs (NSAIDs) are generally safe during pregnancy but should be avoided after 32 weeks of gestation because of their effect on the kidneys that may lead to oligohydramnios[52] and due to the risk of premature closure of the ductus arteriosus[53]. Antihypertensive medications are frequently prescribed in SLE. Women receiving angiotensin-converting enzyme (ACE) inhibitors and angiotensin-2-receptor antagonists should be switched to safer drugs like methyldopa and nifedipine before conception because of the associated fetal renal dysfunction, IUGR, anuria, renal failure and death with second and third trimester exposure[54]. Recently, fetal exposure to ACE inhibitors during the first trimester was also found to be associated with a risk of a major congenital malformation that was 2.7 times higher than that in fetuses exposed to other antihypertensive medications[55].

Women at increased risk for thromboembolic events should be identified, and those with positive aPL antibodies, particularly those with APS, should be started on thromboprophylaxis. However, exact dosages, time of initiation and durations of treatment that optimize fetal outcome have yet to be established[2]. Low-dose aspirin before conception if possible[56] seems to be a reasonable approach for prophylaxis against pre-eclampsia[57] and thrombosis, especially when combined with prophylactic dose low molecular weight heparin (LMWH) or unfractionated heparin at diagnosis of pregnancy[58]. Women with previous thrombosis might require full anticoagulation with LMWH or unfractionated heparin[59]. Women receiving long-term heparin should be supplemented with calcium and vitamin D to prevent osteoporosis[60].

Preconceptional medical evaluation should also include a precise review of the immunological status of the woman including lupus serology (dsDNA and nuclear antibodies), titers of anti-Ro/SSA and anti-La/SSB antibodies and aPL antibodies, serum complement levels (although these are less useful during pregnancy due to a natural increase of C3 and C4 levels[15]), renal function (creatinine, creatinine clearance and 24-h proteinuria) and evaluation of the blood pressure[58,61].

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA), the second most common connective tissue disorder, affects women in their childbearing period with a prevalence of 1 per 2000[61]. RA does not appear to directly affect fecundity or fertility[62]; however, the lower pregnancy rates reported in these women can be explained by its psychosocial effects on childbearing choices[63,64].

How does pregnancy affect RA?

In contrast to SLE, disease activity in inflammatory arthritis such as RA usually improves during pregnancy[65,66]. Over 60% of women report improvement in pain and swelling, and some go into remission, as confirmed in the largest prospective trial on the impact of pregnancy and the postpartum period on RA[67]. The remainder show reduced disease activity in the second trimester, with fewer than 25% showing no improvement or deterioration during

pregnancy[1,67,68]. More recently, de Man and associates, using a validated scoring system, showed a 48% improvement in disease activity during pregnancy in women who had at least moderate disease activity in the first trimester, with a 27% remission rate in the third trimester[69]. Conversely, RA tends to relapse in the postpartum period in 39–70% of cases[64,67,69,70]. Aggravation of disease activity generally occurs within the first 6 months' postpartum[71] when almost all patients show signs of active disease[1].

How does RA affect pregnancy?

The impact of underlying RA on pregnancy outcomes is less well studied. Although some studies do not report any increased risk of adverse pregnancy outcomes in women suffering from RA in terms of rates of spontaneous abortion and risk of low birth weight[72,73], others report increased risk of hypertensive disorders of pregnancy[26,74,75], preterm delivery[72,75], cesarean delivery[26,72,75] and IUGR[26,75]. Reed and colleagues[72] reported on a cohort of 243 women with RA and found an increased risk for prematurity (adjusted relative risk (RR) 1.78, 95% CI 1.21–2.60), cesarean delivery (adjusted RR 1.66, 95% CI 1.22–2.26) but no increased risk for low birth weight after adjusting for gestational age[72]. Similarly, in a national survey of 1425 pregnancies in women with RA, significant increases in the rate of hypertensive disorders (11.1% versus 7.8%; $p < 0.01$), IUGR (3.4% versus 1.6%; $p < 0.01$) and cesarean delivery (37.2% versus 26.5%; $p < 0.001$) were reported. Severe hip arthritis may be an indication for cesarean delivery in some women with RA[76].

Preconception counseling

Women with RA should be evaluated prior to conception, when possible, in order to allow for conversion to safer pharmacologic regimens. Disease improvement during pregnancy often allows for safe discontinuation of potentially harmful agents. Medications that are safe in pregnancy include hydroxychloroquine, sulfasalazine, corticosteroids, NSAIDs prior to 32 weeks of gestation, and anti-tumor necrosis factor agents. Medications that are contraindicated include leflunomide and methotrexate. Since leflunomide may persist in the body for up to 2 years[77], the drug has to be discontinued and eliminated using cholestyramine at least 3 months before attempting pregnancy[64]. Similarly, most experts recommend discontinuing methotrexate 3–4 months before conception to prevent fetal exposure[64].

SYSTEMIC SCLEROSIS

Systemic sclerosis (scleroderma) is not commonly seen in pregnancy, as the mean age of onset is the mid-forties[78]. In these women, sexual functioning may be impaired secondary to Raynaud's phenomenon and dyspareunia[76]. To date, however, studies have not identified decreased overall fertility in these women, but little attempt has been made to relate the timing of pregnancy to the onset of the disease[79–81].

How does pregnancy affect systemic sclerosis?

In general, the disease does not deteriorate during pregnancy if the condition is stable at the time of conception[82]. In one prospective series, 61% of pregnancies had a stable course, 20% experienced some improvement, and 20% had some worsening of symptoms[81]. Symptoms related to systemic sclerosis, particularly Raynaud's phenomenon, improve during pregnancy, but esophageal reflux and shortness of breath on exertion may become worse, particularly during the third trimester[1,81,83]. The third trimester is probably the most critical

period for women with diffuse sclerosis secondary to the adverse effect produced by the enlarging uterus on pulmonary volume and renal function, both of which are already compromised by fibrosis[61]. Mallory–Weiss tears in women with esophageal involvement, who vomit during early or late pregnancy, have been described[1,84]. After pregnancy, some women with diffuse disease have increased skin thickening[81]. The worst complication of systemic sclerosis is renal crisis[85], which does not seem to be influenced by pregnancy[61]. This condition is more common in women with early diffuse systemic sclerosis and should be treated promptly and aggressively with ACE inhibitors despite their contraindication during pregnancy[1,85].

How does systemic sclerosis affect pregnancy?

Reports of pregnancy outcomes in women with systemic sclerosis are limited by the small sample sizes of the published data and conflicting results. Some studies report higher miscarriage rates[83,86] but this observation is inconsistent[79,81]. Case–control studies at single tertiary care centers have shown an increased frequency of preterm births and small for gestational age infants[83,86,87]. In the prospective scleroderma pregnancy study, 91 pregnancies in 59 women were studied[81]. No increased risk for small for gestational age infants was observed despite a significantly higher rate of preterm delivery (29% versus 5%). The overall live birth rate was 84% in women with limited systemic sclerosis, 77% in those with diffuse disease and 84% in historical controls. Earlier studies did not find higher rates of hypertensive disorders of pregnancy in women with systemic sclerosis[86,87]. Recently, however, Chakravarty and associates compared the pregnancy outcome of 504 women with systemic sclerosis to 11.2 million controls. Systemic sclerosis was independently associated with an increased risk of hypertensive disorders (OR 3.71, 95% CI 2.25–6.15) and IUGR (OR 3.74, 95% CI 1.51–9.28)[88].

Preconception counseling

A well-timed pregnancy with careful obstetric monitoring can maximize the likelihood of a successful outcome in women with systemic sclerosis. Because the incidence of a life-threatening renal crisis and other serious cardiopulmonary complications, such as severe cardiomyopathy (ejection fraction <30%), pulmonary hypertension, severe restrictive lung disease (forced vital capacity <50% of predicted), is higher in women who have diffuse sclerosis for less than 4 years, conception should be planned after this period[83,85]. History of renal crisis is not a contraindication to pregnancy provided that the disease has been stable for several years prior to pregnancy[1]. Medication adjustments are less problematic overall compared with other connective tissue disorders, because their use is not as common[76]. Histamine blockers and proton pump inhibitors may be used safely in pregnancy for the treatment of esophageal reflux, nausea and vomiting[89], and intravenous immunoglobulin therapy may be allowed, if needed[45]. Similar to other connective tissue disorders, hydroxychloroquine and corticosteroids can be used safely while cyclophosphamide is contraindicated.

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia diagnosed in the presence of characteristic clinical features including vascular thrombosis, obstetric complications and specified levels of circulating aPL antibodies, namely lupus anticoagulant and anticardiolipin antibodies. APS may be 'primary' or associated with other

autoimmune diseases, particularly SLE. A rare, life-threatening variant of the APS characterized predominantly by small vessel occlusive disease and multiple organ failure is referred to as 'catastrophic APS'. With advances in management, live birth rates of approximately 85–90% have been reported[90].

How does pregnancy affect APS?

Pregnancy is a prothrombotic state owing to increased hypercoagulability[91], hormonally induced decreased venous capacitance and decreased venous outflow[92]. The overall prevalence of thromboembolic events during pregnancy is approximately 2 per 1000 deliveries[93,94]. The risk of arterial thromboembolism, manifest as strokes and heart attacks, is increased three- to four-fold[93,94], while that of venous thromboembolism is increased four- to five-fold[95]. These risks are further aggravated in women with APS[96,97]. Another contributing factor to the increase in the incidence of thromboembolic phenomena in women with APS could be secondary to the discontinuation of warfarin derivatives upon diagnosis of pregnancy by some high-risk women on full anticoagulation due to the fear of fetal malformations. In addition to the increased risk of deep vein thrombosis, pulmonary emboli and stroke, and hepatic infarction have been reported in women with APS in pregnancy and the puerperium[1,98].

How does APS affect pregnancy?

APS is frequently associated with complications during pregnancy such as recurrent early pregnancy loss, as well as late second or third trimester fetal deaths[36,99–102]. Other adverse obstetric outcomes include pre-eclampsia, fetal death, IUGR and preterm delivery. Pre-eclampsia complicates 33–50% of pregnancies with APS[101,103,104]. It is not only more common in women with APS, but also tends to be more severe and to occur at earlier gestational ages compared with normal pregnancies[104,105]; some cases presenting prior to 20 weeks of gestation have been reported[98]. The HELLP syndrome, a specific complication of pregnancy characterized by hemolysis, elevated liver enzymes and low platelets, is more common and more likely to recur in subsequent pregnancies[106]. Although the incidence of HELLP syndrome in women with APS is unknown, Le Thi Thuong and associates[107] found that 53.3% of women diagnosed with HELLP syndrome had APS. IUGR complicates 15–30% of pregnancies in women with APS[103,108,109]. Preterm delivery prior to 34 weeks of gestation may be medically indicated in 37% of women with APS for maternal or fetal indications[103]. Other reported complications include systemic and pulmonary hypertension[42,60].

Preconception counseling

Treatment for APS usually consists of LMWH or unfractionated heparin in combination with low-dose aspirin throughout pregnancy and in the postpartum period, both agents being safe during pregnancy. Most experts advise starting low-dose aspirin (75–81 mg daily) preconceptionally and maintaining it throughout pregnancy. Aspirin has not been associated with an increased risk of congenital malformations[110,111], although some studies report a possible association with gastroschisis due to an increased risk of vascular disruptions[112–114]. Some women with APS and a history of thrombosis or cerebral events are maintained on long-term secondary prophylaxis with oral warfarin derivatives. Because of the known teratogenicity of these latter agents, it is advisable to switch from oral anticoagulants to adjusted dose heparin (either unfractionated or LMWH) before conception or with a positive early pregnancy test and to resume oral anticoagulation therapy postpartum[115,116]. The

preconceptional period is the ideal time to discuss these issues with women with APS.

CONCLUSIONS

Autoimmune and connective tissue diseases commonly affect women of childbearing age. Pregnancy in most of these women is at high risk for maternal and perinatal complications. An optimal obstetric outcome can be achieved only through coordination of care between the obstetrician, maternal fetal medicine specialist, rheumatologist/internist, and, in the case of renal involvement, a nephrologist (Table 1). The consultative process should ideally start prior to conception when women at high risk of pregnancy-related complications are identified and advised not to conceive or to delay conception until their medical condition permits. Medication lists may require some degree of modification in order to avoid the drugs of proven teratogenic effect. On the other hand, some drugs, such as low-dose aspirin, may be appropriate for a select group of women. Establishing a pre-pregnancy plan is

Table 1 The interplay between pregnancy and various connective tissue diseases (CTD)

	Pregnancy effect on CTD	*Effect of CTD on pregnancy*	*Preconception counseling*
Lupus	Exacerbation of disease in up to 65% of patients Risk factors: Renal involvement and active disease within 6 months of pregnancy Pulmonary hypertension: uncommon but increased mortality in pregnancy	**Fetal:** Fetal loss, IUFD, IUGR, preterm delivery, neonatal lupus **Maternal:** Pre-eclampsia, venous/arterial thrombosis, 20-fold increased maternal mortality, cesarean section **Risk factors:** Active disease, renal disease, hypertension, aPL	Pulmonary hypertension and renal failure: contraindication to pregnancy Avoid pregnancy if active disease within 6 months Check blood pressure, renal function, disease activity (complement levels) Assess thrombotic risk (aspirin/heparin accordingly) Check anti-Ro/La serology titers Safe drugs: steroids, azathioprine, cyclosporin A, hydroxychloroquine, NSAIDs*, methyldopa, nifedipine Drugs to avoid: methotrexate, mycophenolate mofetil, cyclophosphamide, ACE inhibitors, angiotensin receptor blocker

continued

Table 1 *continued*

	Pregnancy effect on CTD	*Effect of CTD on pregnancy*	*Preconception counseling*
Rheumatoid arthritis	60% Decreased disease activity/remission <25% No improvement 70% Relapse within 6 months postpartum	Inconsistent across studies Reported effects include: hypertensive disorders, preterm delivery, IUGR, cesarean section	Safe drugs: hydroxychloroquine, sulfasalazine, steroids, NSAIDs*, antitumor necrosis factor agents Drugs to avoid: methotrexate, leflunomide
Scleroderma	60% Stable disease 20% Improved symptoms 20% Worsening symptoms GERD+SOB: Worsen especially in third trimester Raynaud's symptoms: improve Renal crisis†: same as non-pregnant scleroderma population Increased skin thickness postpartum	Inconsistent across studies Reported effects include: miscarriages, preterm deliveries, IUGR, hypertensive disorders	History of renal crisis: not a contraindication for pregnancy Safe drugs: proton pump inhibitor, antihistamines, intravenous immunoglobulins, hydroxychloroquine, steroids Drugs to avoid: cyclophosphamide
Antiphospholipid syndrome	Increased venous/arterial thromboembolism	**Fetal:** Recurrent pregnancy loss (early-late), IUFD, IUGR, preterm delivery **Maternal:** Pre-eclampsia, venous/arterial thrombosis, HELLP syndrome, systemic and pulmonary hypertension	Treatment of antiphospholipid syndrome in pregnancy: aspirin and heparin Low dose aspirin started preconceptionally and maintained throughout pregnancy is advised Warfarin is teratogenic Patients maintained on warfarin therapy should be switched to heparin preferably preconceptionally

*NSAIDs are safe to use in pregnancy before 32 weeks' gestation

†Renal crisis in pregnancy as in non-pregnant patients is managed promptly and aggressively with ACE inhibitors

GERD, gastroesophageal reflux disease; SOB, shortness of breath; IUFD, intrauterine fetal demise; IUGR, intrauterine growth restriction; aPL, antiphospholipid antibodies; HELLP, hemolysis, elevated liver enzymes, low platelets; NSAID, non-steroidal anti-inflammatory drug; ACE, angiotensin converting enzyme

essential in order to anticipate possible complications, prevent them when possible or be ready to act on them as soon as they develop.

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8

Preconceptional counseling for women with chronic kidney disease

Kate Bramham and Liz Lightstone

INTRODUCTION

Chronic kidney disease (CKD) reportedly affects 3% of women between the ages of 20 and 39 years[1]. In view of the increasing age at which many women are now contemplating their first pregnancy, as well as the predicted rise in the number of individuals with CKD due to type 2 diabetes[2], it is likely that CKD will become a more common problem in the offices and clinics of those who provide antenatal care. Under these circumstances, it is essential that health care professionals be aware of the potential complications associated with this condition. Preconceptional counseling for women with CKD allows adequate preparation for pregnancy, both physically and psychologically, as many women may be unaware that their condition has any implications for fetal or maternal health.

NEW DEFINITION OF CHRONIC KIDNEY DISEASE

CKD has recently been redefined according to estimated glomerular filtration rate (eGFR). CKD[3] is said to occur when the eGFR is less than 60 ml/min/1.73m^2, or in the combination of eGFR and abnormal renal structure and/or the presence of proteinuria when the eGFR is more than 60 ml/min/1.73m^2. The eGFR compensates to some extent for the inadequacies of serum creatinine as a marker of renal function, namely its variability with age, gender, ethnicity, diet and muscle mass and its inability to detect kidney impairment until as much as 70% of renal function is lost[4]. The stages of CKD are shown in Table 1. According to epidemiological data from the USA, 3% of women age 20–39 have stage 1 or 2 CKD[5]. It is unlikely that this level of renal impairment affects fertility, so theoretically up to 1 in 30 pregnancies may be complicated by CKD as fewer than 39% of women with stage 1 or 2 CKD have detectable hypertension or proteinuria[5], many women with early CKD are undiagnosed. The modified diet in renal disease (MDRD) formula which is used to calculate eGFR significantly underestimates true GFR in pregnancy as measured by 24 hour creatinine clearance and should not be used in pregnancy[6].

WHO SHOULD RECEIVE COUNSELING?

Pre-pregnancy counseling affords the opportunity to adjust medication, optimize hypertension control, stabilize renal function and educate the woman about the possible adverse events which may arise during or as a consequence of her pregnancy. Although every woman with CKD has an increased risk of pregnancy complications, it is impractical for obstetric nephrologists, obstetric physicians or obstetricians to undertake counseling for

Table 1 Stages of chronic kidney disease (CKD) using the modification of diet in renal disease (MDRD) formula to calculate the estimated glomerular filtration rate (eGFR)

CKD stage	*eGFR* (ml/min/1.73 m²)	*Description*	*Approximate creatinine in non-pregnant women* (μmol/l)
1	>90	Kidney damage* with normal/raised GFR	<70
2	60–90	Kidney damage* with mild/reduced GFR	70–100
3	30–59	Moderately reduced GFR	100–180
4	15–29	Severely reduced GFR	180–350
5	<15	Kidney failure	>350

*Kidney damage with evidence or structural damage or proteinuria; stage 1 or 2 cannot be classified on the basis of GFR alone

every woman with all forms of CKD; therefore, those with mild disease could be managed by their general practitioner (GP) or primary care physician. Table 2 lists certain clinical situations where pre-pregnancy counseling is essential.

Table 2 Women with renal disease who should be referred for pre-pregnancy counseling

- Women with CKD stage 4 or 5
- Women with CKD stage 3 and adverse risk factors, e.g. significant proteinuria, hypertension or previous adverse obstetric history
- Women with kidney transplants
- Women on dialysis who are contemplating pregnancy
- Women with CKD stage 1 or 2 and adverse risk factors, e.g. systemic diseases such as lupus or vasculitis, significant proteinuria, hypertension or previous adverse obstetric history
- Women with a family history of heritable renal disease

CKD, chronic kidney disease

TIMING OF CONCEPTION

One of the essential components of pre-pregnancy counseling is a discussion on the timing of conception, the importance of which varies on an individual basis according to patient age, disease etiology and activity. Evidence from a large series of transplant recipients who subsequently became pregnant identified delaying conception until 12 months post-transplantation was associated with better pregnancy and renal outcomes[7]. A year is now recommended by the European Best Practice Guidelines for care of the renal transplant recipient, to allow for medication adjustments and to reduce the risk of acute graft rejection[8].

Lupus nephritis has also been studied in considerable detail with respect to pregnancy. The risk of disease flare and adverse pregnancy outcomes are increased in women who conceive with active disease[9,10]. Pregnancy and renal complications are significantly reduced in those who have quiescent disease for 6 months prior to conception[11]. It is currently recommended that a period of 6 months after the latest episode of disease flare, including non-renal involvement, pass before attempting to conceive.

Diabetes is independently associated with less than optimal pregnancy outcome, even in women with normal renal function. Hyperglycemia adversely affects rates of preterm delivery, cesarean section, still birth, perinatal mortality and congenital abnormality[12,13]. Hence, women with type 1 as well as type 2 diabetes are advised to optimize their glycemic control before embarking on pregnancy. Similarly, poorly controlled hypertension is a predictor of adverse outcome, and women are advised to delay conception until this is adequately controlled[14], although if renal function is deteriorating rapidly some women may be better advised to conceive sooner rather than later.

The most complicated scenario for advising when to conceive is in an older individual with moderate–severe renal impairment. If the condition is progressive, a younger woman can confidently be advised to wait until she has received a kidney transplant, which will not only improve her fertility, but will increase the chances of a successful, uncomplicated pregnancy. Unfortunately, for women older than 35 years the opportunity for transplantation may not arise until their fertility has declined substantially. For such individuals, the best option, in order to allow her the best possible chance of having a baby at all, is to advise not to delay conception, but to accept that the pregnancy will be high risk.

Contrary to the previously held beliefs of nephrologists and obstetricians a few decades ago that 'children of women with renal disease used to be born dangerously or not at all – not at all if their doctors had their way'[15], there are few situations when conception is not recommended. Such a circumstance requires a complex counseling process, in which the woman needs to be made aware that the chances of a successful pregnancy are very low, and that in commencing pregnancy she will be putting her own health in jeopardy. A powerful argument which may be helpful is a detailed explanation of the life-style adjustments required by renal replacement therapy, together with the anticipated shortened life expectancy, factors which should be important considerations for a potential new mother.

MEDICATION ADJUSTMENTS

Another valuable component of preconceptional counseling for women with CKD is a medication review. Several drugs commonly used by nephrologists and in primary care are teratogenic or have consequences for the fetus later in pregnancy. For the purposes of this discussion, we focus on two major categories: immunosuppressive agents and angiotensin converting enzyme (ACE) inhibitors.

Immunosuppression

Nearly all transplant recipients and many women with glomerulonephritis regularly take immunosuppressive agents. Prednisolone is metabolized by the placenta to relatively inactive 11-ketoforms by 11β-hydroxysteroid dehydrogenase, and only 10% crosses into the fetal circulation at maternal doses of less than 20 mg[16]. Exposure to corticosteroids in the first trimester may slightly increase rates of cleft lip and palate[17,18]; however, this has not been substantiated in all studies[19,20]. Cyclosporine[21,22] and tacrolimus[23] are non-teratogenic; however, there is an increased risk of gestational diabetes in women taking tacrolimus[24], and a glucose tolerance test is recommended at 28 weeks. Azathioprine has also been shown to be safe in pregnancy[25–27].

Mycophenolate mofetil (MMF) is now a first line agent for prevention of allograft rejection and for the treatment of lupus nephritis. Emerging animal data have demonstrated teratogenicity[28], and in 2004 the first case of human teratogenicity was described[29]. Since then 26 cases of early exposure in 18 renal transplant patients have been reported, and a clinical syndrome similar to that found in animal studies has been identified including hypoplastic nails, shortened fifth fingers, diaphragmatic hernia, microtia (ear deformity), micrognathia, cleft lip and palate, and congenital heart defects[30]. These reports, assessed broadly,

resulted in a reclassification of MMF status by the FDA to class C. Women are now advised to switch from MMF at least 3–6 months before conception to an immunosuppressive agent which has a safer profile in pregnancy, e.g. azathioprine, cyclosporine or tacrolimus. There are some clinical situations, however, where alternatives have already been tried without success and MMF is the only treatment able to achieve disease stability. In such a situation the individual needs to be counseled carefully about the relative risks to the fetus if she remains on MMF during her pregnancy. It is currently unknown whether such defects can be detected by antenatal ultrasonography.

Data regarding the use of sirolimus (rapamycin) in pregnancy are limited. Although no evidence of teratogenicity has been identified in animal or clinical studies[30], more information is required before it can be recommended in pregnancy, and women taking sirolimus should be advised to change to an alternative agent at preconceptional counseling.

Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers

Before 2006, exposure to ACE inhibitors in the first trimester was considered acceptable. ACE inhibitors were not advised in the second or third trimester, however, due to an association with fetal complications including growth restriction, oligohydramnios, hypocalvaria, renal dysplasia, anuria, renal failure and often fetal death[31]. However, Cooper *et al*. published a landmark paper in 2005 which suggested that even first trimester only exposure to ACE inhibitors is associated with a 2.7-fold increase in congenital malfomations[32]. Abnormalities include cardiovascular, central nervous system and renal defects.

Three possible approaches are available to women with CKD taking ACE inhibitors/angiotensin II receptor blockers (ARBs) considering pregnancy. Women with minimal proteinuria taking ACE inhibitors/ARBs for blood pressure control can be switched to an alternative antihypertensive known to be safe in pregnancy, e.g. nifedipine, amlodipine, doxazosin, or labetolol. Women with proteinuria controlled by ACE inhibitors/ARBs with mild renal impairment can be advised to stop taking their medication when they start trying to conceive, with close monitoring of blood pressure. However, women with heavy proteinuria, a major adverse indicator of progression of renal disease, risk a marked reduction in GFR if they do not continue to take ACE inhibitors/ARBs whilst they are attempting to conceive. This is particularly difficult for older women, those with more severe renal impairment and those with diabetic nephropathy in whom a prolonged interval without ACE inhibitors/ARBs may be ill advisable. In these cases, it is recommended that ACE inhibitors/ARBs not be stopped preconception but be discontinued as soon as the pregnancy is confirmed, as the period of teratogenicity is considered to be from 6 weeks onwards. Women with an irregular menstrual cycle, in whom pregnancy confirmation may be delayed, need to be assessed and advised on an individual basis.

PREGNANCY AND RENAL OUTCOMES

Women with CKD contemplating pregnancy not only have to be aware of the potential complications of the pregnancy for the fetus, but also of the implications for progression of their renal impairment. Over the past five decades, several mainly retrospective series have attempted to assess these issues. An amalgamation of the data of 908 pregnancies in 676 women is shown in Tables 3 and 4. In view of eGFR being invalid in pregnancy, older classifications according to serum creatinine are used to categorize levels of renal impairment.

Table 3 Pregnancy outcome in 908 pregnancies in 676 women (personal communication, Professor John Davison): risks associated with different levels of renal impairment

Creatinine (μmol/l)	*Problems during pregnancy* (%)	*Successful obstetric outcome* (%)	*Long-term renal problems* (%)
<125	26	96	<3
125–250	47	89	30
>250	86	46	53

Table 4 Pregnancy outcome in 908 pregnancies in 676 women (personal communication, Professor John Davison): type of problem encountered with different levels of renal impairment

Creatinine (μmol/l)	*High blood pressure* (%)	*PET* (%)	*IUGR/Prematurity* (%)
<125	Variable	10–20	Increased
125–250	30–50	40	30–50
>250	Most	80	57–73

IUGR, intrauterine growth retardation

Mild renal impairment (creatinine <125 μmol/l)

Women with mild renal impairment usually have successful pregnancies, although the risk of pre-eclampsia remains greater than background (5%) and should be discussed. Successful fetal outcomes have improved for women with mild renal impairment, and more recently have been reported to be as high as 98%[33]; however, rates of preterm delivery (11–20%) and low birth weight (5–26%) continue to be higher than in healthy controls[14,34,35]. Pregnancy in women with mild renal impairment generally does not precipitate either worsening or an accelerated worsening of maternal kidney function[34,36–39].

Moderate renal impairment (creatinine 125–250 μmol/l)

Fertility is reduced with increasing severity of renal impairment[40]. As many as 1 in 750 pregnancies are complicated by stage 3–5 CKD[41], and the majority of these occur in women with more preserved renal function. The most difficult group of women to give accurate preconceptional counseling are those with moderate renal impairment. Pre-eclampsia may occur in up to 60% of these women[42,43], may occur early and may be severe. An important message to ensure the woman understands is the concept of prematurity, which may occur in 39–64% of women[42–46]. Although major advances in neonatal care have led to marked improvements in survival and outcome, very preterm infants frequently have sensory impairment and intellectual disability. It is therefore important to highlight that there is an increased risk of early complications and hence very preterm delivery which can lead to long-term handicap. Fetal loss is higher in this group of women, with early and late miscarriages not being uncommon[42–46]. A useful early guide to the success of an individual pregnancy is the adaptation to increased GFR[47]. If creatinine does not fall in the late first/early second trimester it is suggestive of future complications.

A very important issue to discuss is the risk of deterioration of renal disease. Renal function may deteriorate in 20% of women

during pregnancy and in an additional 23% between 6 weeks and 6 months postpartum. Some of these women recover their pre-pregnancy renal function values by 6 months, but approximately one-third have a pregnancy-related decline which persists[43]. Even temporary renal deterioration may have serious consequences. In a recent series of 36 women (unpublished data) more than 50% of women with preterm deliveries (<37 weeks' gestation) were delivered iatrogenically due to progressive renal impairment.

Imbasciati *et al*. recently published a comprehensive prospective series of 49 women with mean serum creatinine at conception of 186 ± 88 μmol/l and reported that the most important predictors of permanent deterioration of renal disease were the combined presence pre-pregnancy of GFR of less than 40 ml/min/m^2 and proteinuria exceeding 1 g/24 hours[42]. The authors concluded that both factors need to be present for a statistically significant increase in risk of long-term renal damage[48].

Severe renal impairment (creatinine >250 μmol/l)

Women with stage 4/5 renal disease often have very stormy and unsuccessful pregnancies, with reported rates of fetal and neonatal loss between 24 and 47%[42,46,49], although one more recent series suggests some improvement in these numbers[48]. Pre-eclampsia occurs in the majority of instances, and in recent published case series of women requiring renal replacement therapy, the mean duration of gestation at delivery was 32–33 weeks[50–53]. As previously mentioned, such women have a high risk of deterioration of renal disease, which is likely to result in a need for renal replacement. The life-style implications of dialysis also need to be explained in detail, together with a discussion of shortened life-expectancy. These issues are important for any individual faced with this life changing event, but particularly so for women contemplating bringing up small children.

It is often assumed that women on dialysis never become pregnant due to the negative effects of significant renal impairment on fertility and libido. Many are oligomenorrheic or amenorrheic, but recent data show that 1 in 200 women of childbearing age on dialysis become pregnant[54]. These women are at greatest risk of pregnancy complications and, as such, are one of the most important groups to need thorough and detailed preconceptional counseling. Pregnancy outcomes for those already established on dialysis are worse than for those who require dialysis as a consequence of pregnancy. It is recommended that hemodialysis frequency be increased to 5–7 times per week, aiming for more than 20 hours in order to achieve more normal biochemistry and avoid marked shifts in intravascular volume. This regimen appears to have been successful in several cases[50,51,55]. One of the adverse effects of hemodialysis is the theoretical removal of progesterone from the dialysate, which may be associated with spontaneous preterm labor. An important consideration for these and many other CKD patients is that the obstetric services and nephrology/dialysis facilities need be on the same site. In an ideal world, there would be close communication between the senior care providers of both services and, if there were large numbers of patients being seen by both services, a bi-weekly joint care conference or regular joint care clinics could facilitate this communication.

The number of pregnant individuals on peritoneal dialysis (PD) is approximately two to three times lower than that of those on hemodialysis[56,57]. This is postulated to be due to the hypertonic peritoneal milieu and volume of fluid in the abdominal cavity having adverse effects on the ovum or its transport down the fallopian tubes[40,58] as well as previous episodes of peritonitis resulting in adhesions and failure of implantation[57]. No robust direct

comparison exists between dialysis modalities in pregnancy; however, babies born to mothers on PD have higher birth weights, and there is less pre-eclampsia, whereas premature labor and peritonitis are more common[58]. However, the majority of women who conceive whilst on PD are often changed to hemodialysis due to perceived issues of volume, inadequate clearance and less experience worldwide upon which to draw.

Women who already require erythrocyte stimulating agents are likely to need larger doses throughout gestation, and some women may develop erythropoietin deficiency during pregnancy due to failure of endogenous synthesis to meet the increased demands.

PROTEINURIA

Proteinuria increases in normal pregnancy due to increased GFR and alteration in renal handling. The upper limit of normal proteinuria is doubled in pregnancy to 300 mg/24 hours or 30 mg/μmol creatinine[59]. Up to 30% of women with CKD without proteinuria pre-pregnancy develop proteinuria during pregnancy[60], and those with pre-existing proteinuria may have a dramatic increase in urinary protein loss reaching nephrotic levels in some cases[14]. Some authors report that the presence of proteinuria in pregnancy is associated with a worse outcome, although this is not a consensus view.

If proteinuria reaches nephrotic range (>3 g/24 hours), with serum albumin <30 g/dl, it is advised by consensus expert opinion that women should be commenced on thromboprophylaxis, due to the theoretical loss of antithrombin in the urine and associated changes in coagulation factors[61]. Dosing of low molecular weight heparin should be prescribed according to the level of renal impairment. Women with pre-pregnancy proteinuria should be warned of this possibility, as the concept of daily injections can sometimes be alarming to unprepared individuals.

HYPERTENSION

Pregnancy is a state of systemic vasodilatation in healthy individuals, but in those with chronic hypertension and/or pre-existing CKD this may worsen, or arise *de novo* requiring multiple antihypertensive agents. Hypertension itself is associated with a worse pregnancy outcome in women with CKD[14,62]. It is noteworthy that the absence of hypertension, almost regardless of renal function, predicts the best outcome. The distinction between progressive hypertension and proteinuria and the development of pre-eclampsia can often be difficult in the presence of CKD, and may require admission for observation. Serial growth scans are often performed in women with moderate/severe renal impairment, which helps guide the obstetrician to make decisions about delivery; however, women need to be forewarned that a degree of uncertainty may occur with this complex clinical problem.

URINARY TRACT INFECTION

During pregnancy urinary tract infections (UTIs) are more common, due to the dilatation of the urinary tract and subsequent urinary stasis. Women with CKD are at particular risk of developing UTIs and appropriate advice regarding symptom detection and screening should be given in preconceptional counseling.

CONSIDERATIONS FOR INDIVIDUAL ETIOLOGIES OF CHRONIC KIDNEY DISEASE

Lupus nephritis

Some women with lupus nephritis may have received cyclophosphamide which can lead to ovarian failure. This may be of concern to those women now wanting to conceive, but the majority can usually be reassured, as the

adverse effects of the drug on fertility are determined by the age of the woman at the time of treatment and the amount of cyclophosphamide received[63,64]. However, exposure to cyclophosphamide can be associated with premature menopause. Hence, whilst as previously mentioned it is important for lupus nephritis to be quiescent for 6 months prior to conception[11], women with prior exposure to cyclophosphamide should be referred promptly to infertility specialists if there are delays in conceiving thereafter. A flare of lupus nephritis may often be difficult to differentiate from the development of pre-eclampsia, but certain clinical and laboratory features, e.g. rising dsDNA, may help to distinguish between the two conditions. At earlier gestations where fetal viability is paramount, a renal biopsy may be needed to inform further treatment decisions. Although biopsy is no less safe than in the non-pregnant state, in the majority, and certainly beyond 24 weeks it can usually be avoided. Women with lupus nephritis tend to have worse pregnancy outcomes than women with the same level of renal impairment with different etiologies[60]. The reason for this finding is unclear, but may be related to the systemic nature of the disease.

Transplantation

Renal transplant recipients form a large proportion of women with CKD who contemplate pregnancy due to the restoration of both fertility and libido with renal function[65]. A period of 1 year after transplantation is recommended, and MMF and sirolimus should be avoided as discussed previously. Women should be reassured that there is no conclusive evidence that pregnancy increases the risk of graft rejection, or causes a deterioration in graft function[7,66–69], other than in those with moderate–severe renal impairment[70]. This group of women may already have experienced renal replacement therapy and are often more reluctant than those at the same stage of renal impairment without renal transplants to pursue pregnancy if they consider their graft to be at risk. Unfortunately, women with excellent graft function and 'normal' GFR still have an increased risk of pre-eclampsia[62,67,68], potentially due to previous endothelial injury or undetectable graft fibrosis. Handling of calcineurin inhibitors alters during pregnancy, and levels need to be monitored closely as women may need an increase of up to 40% of pre-pregnancy doses.

Urinary tract infection is common in the presence of a renal transplant, and women should be advised to seek medical advice at the first suspicion of symptoms. Monthly screening for asymptomatic bacteruria is advised by European Best Practice Guidelines (EPBG) and, for those with recurrent infection, prophylaxis throughout the rest of pregnancy is recommended[8]. Women with renal transplants should be reassured that they can have normal vaginal deliveries and that the allograft will not be damaged by pregnancy or delivery due to its anatomical position.

Reflux nephropathy

Reflux nephropathy is a common cause of renal impairment in women of childbearing age. It complicates pregnancy due to the increased frequency of UTIs, but is not associated with any additional risk of complications with regards to the level of renal impairment. If there is evidence of vesicoureteric reflux in the mother, this should be screened for in the child as soon as possible after birth[71], though some cases may be detected *in utero*.

Adult polycystic kidney disease

In common with women with reflux nephropathy, women with adult polycystic kidney disease (APKD) may also experience more UTIs, as well as bleeding into cysts. It is very unlikely that the size of the kidneys will preclude pregnancy, and women can often be reassured in this regard. Women with known APKD should be advised of the genetic risk to their offspring (1 in 2). However, few if any women contemplate termination. The situation is more challenging when women present for the first time with APKD during the first trimester of their pregnancy.

CONCLUSION

Women with CKD are a diverse group of individuals with a spectrum of pregnancy outcomes, from those with a minimal increase in risk of pre-eclampsia, to those very unlikely to have a normal pregnancy course. One of the most useful guides to pregnancy outcome is obstetric history, as future pregnancies often mirror previous pregnancies.

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9
Inherited thrombophilic disorders

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INTRODUCTION

Inherited thrombophilia is thought to increase the risk of pregnancy related venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE).

Pregnancy is a hypercoagulable state due to the increased concentration of coagulation factors, decreased natural anticoagulants and fibrinolytic activity[1]. The pregnant woman is therefore at increased risk for VTE and this predisposition is much accentuated in patients with thrombophilia. Thus it is important to identify this group of patients before or early in pregnancy in order to tailor appropriate preventive means.

THE APPROACH TO VENOUS THROMBOEMBOLISM

The clinical approach to acute VTE is the same in patients with or without inherited thrombophilia. However, most patients with a confirmed episode of VTE will eventually undergo thrombophilia screening if acquired causes are excluded. Obviously, the clinical utility of testing is the a priori assumption that the test results are likely to improve health outcome. In this context, one should remember that screening is performed in the absence of disease, whereas testing is performed in the presence of symptoms or signs. It follows that in the case of thrombophilia the actual workup is for testing rather than for screening.

In contrast to the simple, reliable and inexpensive laboratory tests used to investigate bleeding disorders such as prothrombin time (PT) and partial thromboplastin time (PTT), no such diagnostic means exist for testing/screening of hypercoagulable states. Moreover, the literature holds that thrombophilia testing/screening is expensive. For example, Wu and colleagues[2] calculated the incremental cost-effectiveness ratio (ICER; the lower the ICER the more cost-effective the strategy to avoid a major adverse clinical outcome) for universal screening prior to prescribing combined contraception, for example, is as high as £202,402 (UK), whereas for hormone replacement it is far less (£6824) (UK). Stated another way, it is not cost-effective to perform routine thrombophilia screening before prescribing hormonal therapy. Several authorities have maintained that screening the general population is not justified mainly because of the above mentioned financial considerations[3–5]. Therefore, in order to avoid indiscriminate thrombophilia screening and waste of health resources, one must consider the indication, advantages and pitfalls of such an investigation. Injudicious thrombophilia screening should therefore be discouraged.

Every testing/screening should be based on the prevalence of each inherited thrombophilic condition and the association of each with the risk of VTE. Several inherited thrombophilic conditions predispose to venous thrombosis. The most important are factor V Leiden mutation, prothrombin gene mutation, protein C,

protein S and antithrombin deficiency, elevated factor VIIIc and hyperhomocysteinemia[6]. The frequency of the natural anticoagulant protein S, protein C and antithrombin deficiencies is low in the general population (<1% in total) as well as in patients with VTE (5% in total), but the frequency of gain of functional mutations – factor V Leiden and prothrombin gene mutation – is common in the general population (3–7% and 3%, respectively) as well as in patients with VTE (25% and 10%, respectively). The prevalence of factor V Leiden and prothrombin gene mutation is 10–15% in the Caucasian population but increases to about 50% in patients with recurrent thromboembolic phenomena.

Because selection for thrombophilia testing/screening is required, a rather long list of candidates has been created over the years. To simplify this list, these candidates have been grouped under three subheadings[7–21].

Venous thromboembolism

Age is the single most important factor for VTE, and hence, young patients (defined as <50 years) who experienced previous VTE after an event that is no longer present, such as minor surgery or bone fracture, should undergo evaluation. However, even if there is no identifiable risk factor for VTE, *patients with unprovoked VTE at any age*, should be screened for thrombophilia. Similarly, the association of VTE in the absence of any other risk factor except the use of *exogenous estrogens* (oral contraception and hormone replacement) or *pregnancy*, should lead to screening, as is the case for patients with *recurrent VTE at any age* or *early age of onset*. In addition to the common sites of DVT, it has been suggested that patients with *superficial thrombophlebitis* without malignancy and those with *DVT at unusual sites* (cerebral, mesenteric, portal or hepatic) under the age of 50 years also should be evaluated. This category includes the rare event of a neonate with *purpura fulminans* without sepsis. Because this circumstance is suspected to manifest a homozygous state of protein C and S deficiencies, first degree relatives should also be screened.

Warfarin decreases the level of the natural anticoagulant protein C and S, as well as vitamin K-dependent coagulation factors. In some patients receiving warfarin, the decrease in anticoagulants is faster than the decrease in coagulation factors, and they develop skin necrosis. Accordingly, patients who sustained warfarin skin necrosis are suspected to be heterozygous for protein C and S deficiency and should therefore be investigated.

Family history

Patients with **first degree relatives** who have had a VTE at a young age or as a pregnancy complication are candidates for screening.

Previous adverse pregnancy outcomes

The association of some adverse pregnancy outcomes with inherited thrombophilia is controversial. Since placenta-mediated pregnancy complications are thought to result from placental micro/macrothrombosis in blood vessels, one might assume that thrombophilia should increase thrombotic risk. However, conflicting data exist for the link between pregnancy complications and thrombophilic risk factors. A recent meta-analysis of 25 studies on 11,183 women found a significant association between pregnancy complications and thrombophilia, especially for early and late recurrent pregnancy loss associated with antiphospholipid antibodies (APLA), factor V Leiden and the prothrombin gene mutation[13].

Data evaluation demonstrated a strong association between factor V Leiden and recurrent pregnancy loss, as well as severity of pregnancy complications in the second and third trimesters compared to first trimester. The

evaluation, however, indicates that the relationship between thrombophilia and pregnancy complications is confounded by ethnicity, severity of illness and method of testing[14].

In contrast, other recent studies failed to demonstrate an association between thrombophilia and adverse pregnancy outcome[15–25]. While thrombophilias are associated with placental-mediated pregnancy complications, their *causal contribution is weak*. The association makes biological sense (consistent with the pathophysiological theory of the development of pregnancy complications) but the association is inconsistent, non-specific, without biological gradient and with no convincing evidence from clinical studies for causal association[18,21]. Publication bias also plays a role in the interpretation of findings in relevant studies.

It is therefore not surprising that the latest American College of Chest Physicians (ACCP) guidelines on VTE, thrombophilia and antithrombotic therapy recommend that only women who have had recurrent early loss (three or more miscarriages), unexplained late pregnancy loss, and severe or recurrent pre-eclampsia or intrauterine growth restriction (IUGR) be screened for APLA[26].

WHEN TO TEST FOR THROMBOPHILIA?

Coagulation factors and natural anticoagulation levels change during acute VTE, under specific medication and during pregnancy[7,27,28]. Biochemical evaluation can be postponed until the treatment duration (3–6 months) for an acute VTE is over, whereas polymerase chain reaction (PCR) tests for factor V Leiden and factor II mutation can be performed at any time. Similarly, lupus anticoagulant (LAC) and APLA levels do not change with acute VTE, but should be re-confirmed after a 12-week interval.

Clot based assays like protein S and factor VIII should not be performed during the acute phase of VTE, during pregnancy, or during oral contraception and warfarin treatment. Tests should be performed at least 2–3 months after pregnancy and withdrawal of oral contraception, and 1 month after warfarin treatment is completed.

Antithrombin levels may be determined during acute VTE before unfractionated heparin (UFH) or low molecular weight heparin (LMWH) treatments are initiated, as both interact with antithrombin. This is because antithrombin concentrate replacement may be necessary for acute VTE, together with heparin or LMWH treatment for severe antithrombin deficiency.

Screening seems to be unnecessary in patients on prolonged anticoagulant treatment (malignancy or recurrent VTE) because the decision for treatment has already been made. Likewise, in patients with a personal or familial VTE history, there is no need for routine preoperative screening, as the results will not change the recommended thromboprophylaxis policy in most of them[7].

WHY PERFORM THROMBOPHILIC TESTS?

The rationale to perform thrombophilia testing is mainly to establish the genetic basis of the VTE[5,29]. Once known, the etiologic factor or presence of combined defects may be communicated to the patients and may influence the duration of treatment and establish the potential risk for recurrence. This knowledge also may help in providing thromboprophylaxis to high-risk patients and their first-degree relatives.

One potential advantage of thrombophilia testing is for consulting women with a personal or significant family history of VTE who may wish to use oral contraception, HRT, or to become pregnant. Advantages of testing are

more pronounced among women considering HRT than oral contraception, because of the much higher risk of VTE in middle-aged women. Ancillary advantages of family screening are to provide additional health benefits such as controlling blood pressure, lipid disorders, obesity and smoking.

From a scientific point of view, recognizing the prevalence of thrombophilia in minorities[30] or in certain disease conditions unrelated to VTE or pregnancy complications may improve the true impact of such conditions in terms of public health.

WHY NOT PERFORM THROMBOPHILIA SCREENING?

Numerous arguments exist against screening for thrombophilia[31–33]. The arguments related to the inaccuracy in establishing the correct laboratory diagnosis are beyond the scope of this chapter[28,29]. Nor is the problem related to websites promoting genetic testing for thrombophilia without physician supervision. However, other relevant opinions should be heard.

First and foremost is the fact that in most cases the decision about duration and intensity of anticoagulant therapy can be made by clinical criteria without actually knowing the underlying cause. In simple terms, VTE patients with or without thrombophilia will be managed in a similar way in most cases.

Second, controversy exists regarding the ability of a given defect to predict which patient is likely to have a recurrent VTE[32]. Stated differently, the presence of a positive test of several thrombophilias does not necessarily mean an increased risk of recurrence[34]. Conversely, concern has been voiced that unnecessary testing may overestimate the risk with consequently needless and potentially hazardous treatment. In this respect, it is important to note that in the absence of randomized controlled trials that support treatment during pregnancy, one may question the wisdom of screening patients with adverse pregnancy outcomes.

Third, the arguments related to the cost-effectiveness of routine universal screening are cogent. For example, one would need to screen 2 million women for factor V Leiden before starting oral contraception in order to prevent one death from pulmonary embolism[35].

Fourth, there is a definite psychological effect of screening stress which may affect quality of life in patients with a potential rather than with a real risk. For example, a positive thrombophilia test does not necessarily mean VTE in the future, as 40% of women tested positive will never develop VTE[36]. Conversely, false reassurance is unjustified in a patient with negative testing merely because our understanding of the coagulation cascade is incomplete, and the availability of commercial laboratory kits is limited. For example, protein Z deficiency or antibodies are known thrombophilic factors, but their assessment is vastly limited because the laboratory methodology is not widely available.

Finally, as noted above, a patient with a positive test may never have any health problem. Yet, some insurance companies may be reluctant to insure this patient or may increase the cost involved.

Preconception consulting for women with a history of pregnancy complications and documented thrombophilia should include the controversy of the association between the genetic defects and pregnancy outcome. It must be emphasized, however, that at present the association between thrombophilia and adverse pregnancy outcome is unclear, as thrombophilias are only weakly associated with adverse pregnancy outcomes. It appears that thrombophilias are but one of many factors involved in poor obstetric outcome.

WHAT IS THE MOST ECONOMICAL WAY TO SCREEN FOR INHERITED THROMBOPHILIA?

One way to reduce the costs of screening/testing is to look for specific thrombophilia factors rather than to test for every known factor for which a test is available. Table 1 shows the list of tests according to priority, which is set by the likelihood of inherited thrombophilia in a given case[28]. The highest diagnostic yield is expected with the high priority tests mainly because they are also the most frequent.

Other inexpensive and useful means for screening patients with hypercoagulable states and pregnancy complications have been reported recently. The ProC Global assay is one that globally evaluates the functionality of the protein C pathway[37–40]. The assay is based on the ability of endogenous activated protein C (APC), generated by a snake venom extract, to prolong an activated partial thromboplastin time (APTT). This assay can distinguish patients with or without protein C pathway abnormalities. It has been reported that the ProC Global assay can be used as the initial step in screening for factor V Leiden-related APC resistance and protein C deficiency in patients who are not on oral anticoagulants. This assay, however, has low sensitivity to protein S deficiency. The ProC Global test is claimed to screen for women with idiopathic pregnancy loss[39] and to identify patients at increased risk for VTE[40].

ANTITHROMBOTIC THERAPY DURING PREGNANCY

Anticoagulation is indicated during pregnancy for the prevention of VTE, treatment of acute VTE, prevention of emboli in patients with mechanical heart valves, and in prevention of recurrent pregnancy loss in women with APLA.

Available antithrombotic drugs include UFH and LMWH, and the antiaggregant agent commonly used is aspirin. LMWH is recommended over UFH for the prevention and treatment of VTE during pregnancy[26]. UFH treatment has significant side-effects such as osteoporosis and heparin-induced thrombocytopenia (HIT), and requires laboratory monitoring. These side-effects are significantly less common with LMWH, and there is no need for routine laboratory testing during treatment (except for the infrequent need for dose-adjustments by measuring anti-Xa). LMWH has better bioavailability, longer plasma half-life and an improved safety profile over UFH according to the 8th edition of ACCP guidelines[26].

UFH and LMWH do not cross the placenta and are not secreted in breast milk. A recent review showed a good safety profile of

Table 1 Testing according to high, intermediate and low priority of thrombophilia factors. Adapted from reference 28

High priority	*Intermediate priority*	*Low priority*
APCR	Protein C activity	Dysfibrinogenemia
Factor V Leiden	Free protein S	Elevated fibrinogen level
Factor II mutation	Decreased antithrombin activity	Increased activity of factors IX and XI
Elevated homocysteine level	Increased anticardiolipin antibodies	MTHFR
Elevated factor VIII level		
Lupus anticoagulant		

APCR, activated protein C resistance; MTHFR, methylenetetrahydrofolate reductase

enoxaparin during pregnancy[41]. In particular, the rates of bleeding complications and osteoporosis were low, and there were no cases of heparin-induced thrombocytopenia (HIT).

Women with a history of VTE or thrombophilia have an increased risk for pregnancy associated recurrent VTE[42], but no large clinical trials have assessed the role of prophylaxis in pregnant women with previous VTE. Retrospective and prospective studies demonstrated a good pregnancy outcome for women with previous VTE whether or not treated by heparin prophylaxis[43,44]. This, however, was not true for women with APLA who are at high risk of VTE, pregnancy loss and pre-eclampsia[45]. Data demonstrate that women with APLA and recurrent fetal loss have an improved pregnancy outcome when treated with combined therapy consisting of low-dose aspirin and heparin prophylaxis[46]. In contrast, a randomized trial failed to confirm an improved pregnancy outcome by adding heparin to aspirin in this specific population of women[47].

Several meta-analyses have been performed to investigate the association between thrombophilia and pre-eclampsia[48–50]. Factor V Leiden, MTHFR 677C>T polymorphism and other inherited thrombophilias were found to moderately increase the risk of pre-eclampsia, but the link is weak and routine screening for thrombophilia is not recommended. The effect of aspirin on the recurrence of pre-eclampsia has been studied in large trials, but no such trials have been performed with LMWH.

Small and uncontrolled studies on treatment with LMWH of women with inherited thrombophilia and pregnancy loss have suggested that prophylaxis with enoxaparin is effective (and safe) in improving pregnancy outome and has a potential for reducing late pregnancy complications[51,52]. Two recent randomized controlled trials[53,54] demonstrated *no reduction* in pregnancy loss rate with antithrombotic intervention in pregnant women with two or more unexplained recurrent pregnancy losses. At present, women with a history of placenta-mediated pregnancy complications, with or without genetic thrombophilia, should not be treated routinely by anticoagulants, unless in the context of randomized controlled trials.

To date, no clear criteria or guidelines exist for the diagnosis and treatment of women with thrombophilia in pregnancy. Physicians may treat these women based on clinical judgment and on their own experience.

The most recent guidelines on VTE, thrombophilia, antithrombotic therapy and pregnancy were published by the ACCP[26] and the Royal College of Obstetricians and Gynaecologists in 2009[55]. The recommended thromboprophylaxis in pregnancy can be divided into two subgroups.

1. Prevention of recurrent VTE in pregnancy:
   a. A previous VTE event associated with a transient risk factor and no thrombophilia: clinical surveillance antepartum and anticoagulant prophylaxis postpartum;
   b. A previous VTE event associated with pregnancy or estrogen containing drug: antepartum clinical surveillance or prophylactic/intermediate-dose anticoagulant prophylaxis (LMWH/UFH) plus postpartum prophylaxis;
   c. Single idiopathic VTE event without thrombophilia: prophylactic/intermediate-dose anticoagulant (LMWH/UFH) or clinical surveillance antepartum plus postpartum anticoagulant;
   d. Single episode of VTE and laboratory confirmed thrombophilia without long-term anticoagulants: prophylactic/intermediate-dose anticoagulant (LMWH/UFH) or clinical surveillance antepartum plus postpartum anticoagulant;
   e. Single episode of VTE and high-risk thrombophilias (antithrombin deficiency, APLA, compound heterozygote for factor V Leiden and prothrombin mutation, homozygosity for these mutations) not receiving long-term anticoagulants: prophylactic/intermediate-dose anticoagulant (LMWH/UFH) antepartum plus postpartum anticoagulation;
   f. Multiple episodes of VTE not receiving long-term anticoagulants: prophylactic /intermediate/adjusted-dose anticoagulant (LMWH/UFH) antepartum plus postpartum anticoagulants;
   g. Long-term anticoagulants for prior VTE: frequent pregnancy tests and substitution of adjusted/intermediate-dose UFH/LMWH when pregnancy is achieved. Postpartum, long-term anticoagulants should be resumed;
   h. All women with previous VTE are advised to use graduated compression stockings;
   i. Women with thrombophilia and no prior VTE: individual risk assessment;
   j. Antithrombin deficiency and no history of VTE: antepartum and postpartum prophylaxis. Other thrombophilias without prior VTE: clinical surveillance or prophylactic anticoagulants (LMWH/UFH) antepartum plus postpartum anticoagulants.
2. Prevention of recurrent pregnancy complications in women with thrombophilia:
   a. APLA and three or more events of pregnancy loss, no VTE or arterial thrombosis: antepartum prophylactic/intermediate UFH/LMWH, combined with aspirin;
   b. High risk for pre-eclampsia: low-dose aspirin throughout pregnancy;
   c. History of pre-eclampsia: UFH/LMWH is not recommended for subsequent pregnancies.

A woman with previous VTE or pregnancy complications, who wishes to get pregnant again, needs the consultation and co-management of an obstetrician, hematologist and coagulation expert. This team should counsel the woman about the recommended diagnostic tests, suggest available treatment protocols and supervise the subsequent pregnancy.

SUMMARY

Until we find useful and inexpensive screening tools, it is not recommended to test every patient or her/his relatives for thrombophilia. Screening should be limited to patients at high-risk of VTE. Each index case should be carefully evaluated by an expert physician who should tailor the laboratory testing as well as treatment modalities.

Thrombophilias are considered to be only weakly associated with adverse pregnancy outcome and are but one of many factors involved in such circumstances. At present, women with a history of placenta-mediated pregnancy complications, with or without genetic thrombophilia, should not be treated routinely with anticoagulants, unless in the context of randomized controlled trials.

In order to optimize the diagnosis and treatment of pregnant women with thrombophilia and previous VTE or pregnancy complications, a team made up of an obstetrician, hematologist and coagulation expert seems essential.

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10

Preconceptional counseling in women with inflammatory bowel disease

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INTRODUCTION

Inflammatory bowel disease (IBD) is a generic term which predominantly describes two chronic inflammatory bowel conditions, namely ulcerative colitis (UC) and Crohn's disease (CD). IBD is characterized by a bimodal pattern of presentation with the first peak occurring in younger patients between the ages of 15 and 45 years. As such, it coincides exactly with the reproductive age[1]. The second peak occurs between 60 and 80 years of age. Ulcerative colitis and Crohn's disease can affect both males and females.

The presence of IBD, the degree of disease activity when conception is desired, the type(s) and quantity(ies) of medication used before or during the pregnancy, as well as any surgery used as part of the management of the condition, all can exert a profound effect on trying to conceive as well as pregnancy outcome. At the same time, pregnancy itself can affect the underlying bowel condition in the female.

UC is an inflammatory bowel condition affecting the large bowel and presenting with continuous inflammation, with or without superficial ulceration, of the mucosal lining. The rectum is nearly always involved in UC, and the inflammation may extend for a variable distance proximally. When the entire bowel is involved, the condition is called pancolitis as opposed to proctitis if the rectum only is involved. UC is common in the north European population, with a prevalence of 100–200 and an incidence of 10–20 per 100,000 persons[2,3]. Incidence varies amongst different ethnic groups; for example, Ashkenazi Jews have a higher incidence compared to non-Ashkenazi Jews. In some populations, such as the Japanese, the incidence is very low.

CD, in contrast to UC, can affect both small and large bowel. Moreover, the disease is often discontinuous with so-called skip lesions in which severely inflamed sections of bowel can be immediately adjacent to non-inflamed segments. The inflammatory process is both granulomatous and transmural, and can lead to stricture formation or fistulization between adjacent loops of bowel (entero–entero fistula), other organs such as the bladder (enterovesical fistula), the vagina (enterovaginal fistula) or the skin, especially the perineum can be affected. The inflammatory process can also cause inflammation and subsequent blockage of the fallopian tubes, a feature which may permanently affect fecundity. The incidence and prevalence of CD is approximately half that of UC, but whilst the statistics for UC are static, they are increasing for CD. Although many similarities are present with regard to the types of medication used to treat UC and CD, major differences are also present with important implications for conception and successful outcome. This is particularly true if surgical management has been part of the treatment armamentarium. Disease activity

and the severity of such activity relative to the time of conception also affect the chances of a successful outcome. Because the variables and their combination(s) that impact conception are numerous, it is important to use an individualized approach for each couple thinking about starting a family. Generally the female with IBD seeks counseling prior to contemplating conception, but occasionally a disease-free woman seeks help because the intended father of her child has some form of IBD and she or they are concerned that this may impact the decision or ability to conceive. In either case, it is important to recognize that patients with chronic conditions such as IBD often have experienced negative effects as regards their quality of life and have issues meriting discussion in advance of making such a life-changing decision[4,5]. All too often, these concerns are unvoiced and health-care providers should provide ample opportunity for patients and their partners to vocalize their concerns in the context of a tactful and sensitive discussion.

MANAGING EXPECTATIONS – A BESPOKE CLIENT CENTERED TEAM BASED APPROACH

It is easily appreciated that what for anyone represents a potentially anxious time is even more so for patients with IBD who plan or manage to conceive. Simply put, such patients are worried about what will happen and have recurring questions including:

- Is it going to be difficult to become pregnant because of my medical condition?
- Is there a chance of my baby having IBD?
- Is it more likely that my baby will have a malformation?
- Is it possible that my medications will harm the baby?
- Is it alright to stop my medication before trying to conceive?
- Is it alright to take my medication during pregnancy?
- Is the condition more likely to flare up whilst I am pregnant?
- Is it alright to take stronger medications if I have a flare up?
- Is the surgery I had going to affect my chances of conceiving?
- Is my condition such that I can't deliver normally?
- Is it possible to breastfeed if I am taking these tablets?
- Is it going to be alright, doctor?

Given these circumstances, it follows that a team approach should be adopted from the earliest stages with the patient (and partner) central to any decision making. For this to occur, the patient must be confident that:

1. She can contact the team at any time – usually this means by phone in the first instance, with the knowledge that she can be seen rapidly in clinic if need be. To easily accomplish this, the patient must be provided with the number of a contact person who she has met before, is always available and the patient can trust. In the UK this is usually a nurse specialist working with the gastroenterologist. Another important role for the specialist nurse is to act as liaison facilitator enabling all parties to co-ordinate their efforts.
2. She can get the same consistent message from the various parties involved in her care rather than contradictory advice from random health-care workers peripheral to her care. This means that *for quality care only senior members of the health-care team should be involved,* because junior team members may lack the in-depth knowledge or not understand the intricacies and subtleties around the pregnant woman with a difficult and often unpredictable condition.

3. The obstetrician, medical gastroenterologist and surgical gastroenterologist are clear in their focus and signed up to the same management plan. Nothing causes as much stress as being on the receiving end of mixed messages.

ISSUES TO BE ADDRESSED DURING PRECONCEPTION COUNSELING

Lifestyle

In addition to the advice that would be provided to any woman contemplating conception, patients with IBD need to consider the following.

Smoking

Smoking cessation help should be offered to all women. Not only is smoking associated with intrauterine growth retardation and smaller babies, but also in patients with CD it is associated with a greater likelihood of relapse and slower treatment response.

Nutrition

Patients with IBD whose disease has been active often have some evidence of nutritional deficits in trace elements, iron stores or vitamins. This is especially true for those with CD. Therefore, early attention to this is especially important. Folic acid supplementation is routinely advised in all women, but is essential in patients with CD who may already be deficient and any IBD patient who has been on sulfsalazine which is a folic acid antagonist. Folic acid supplementation should be started in the preconception period, as the neural tube closes by the 28th day of pregnancy and supplementation begun after that day cannot be relied upon to prevent neural tube defects (see Chapter 22).

Inheritance

Patients with IBD are usually quite aware of the genetic component to the condition, with UC and CD sufferers both reporting having first degree relatives with some IBD with a frequency ranging from 8 to 13.8%[6–10].The degree of concordance is greater with CD rather than UC. Studies of monozygotic twins in north European countries show a concordance of 20–50%, whereas for dizygotic twins the figure is only 3–7%[11–14]. The degree of concordance in UC is lower than that for CD. The fact that the concordance is not 100% in monozygotic twins supports the theory that genetics is just one of several components contributing to the etiology of IBD and that other factors which we do not fully understand also are present.

Most patients simply ask the question: 'What's the risk of us having a baby with ulcerative colitis or Crohn's disease?' This point needs to be discussed frankly with the patient and her partner. How the patient is counseled is important, as there is a tendency to focus on the negatives rather than the positives.

The risk of any offspring having some form of IBD depends on whether one or both parents suffer with the condition. Ethnicity is also a factor, as Jewish populations have a higher incidence of IBD than non-Jews. Yang's empirical study of the observed familial life time risks of developing IBD in a South Californian population revealed that the risks were 1.6% and 5.2% for non-Jews developing UC or CD, respectively[15,16]. However, for Jews the risks were considerably higher being 4.5% and 7.8% for UC and CD, respectively. If both parents suffer with IBD, then the chances are considerably greater at 36%.

Because patients or couples need easily understandable facts and figures to take away

and think about, I generally phrase the risks as follows. If only one of the parents has IBD, the chance of having a child without IBD is approximately 95%. For Jewish patients, the ballpark figure for being disease free is 90%. If both parents have IBD, the chance of the offspring being IBD disease free all their life is only 65%.

Fertility and fecundity

Definition

Unfortunately, even amongst clinicians there exists an opacity with regards to the correct use of these terms which are often used interchangeably. This circumstance has not been helped by demographers who refer to the ability of having babies as fecundity and the rate at which women actually have children as fertility; biologists and clinicians, on the other hand, seem to use the terms the other way around, namely saying that fertility is the theoretical capacity to have offspring, whereas fecundity is the actual realization of this, i.e. producing live born. To understand the differences seen between patients with active IBD, especially CD, and those with inactive disease, the use of the biologists' definition of fecundity and effective fecundity is revealing. Wood states that fecundity reflects both a woman's ability to conceive and her ability to carry the pregnancy to full term[17]. This author goes on to itemize some factors affecting ability to conceive which are of direct relevance to the IBD patient. These include not only what is referred to as 'susceptibility factors' such as the age of onset of menarche and menopause, but also pathological sterility – a factor in CD where inflammation of the fallopian tubes from adjacent inflamed loops of bowel may cause blockage. There are also 'fecundability' issues which include, amongst other things, duration and number of ovulatory cycles, which again are often affected by severe flare ups of IBD and fetal loss.

Voluntary childlessness and fear

Mountfield *et al*., working with a group of Australian women with IBD, studied the issue of 'voluntary childlessness' by means of a detailed questionnaire[18]. Among respondents, 42.7% described a fear of infertility which was more marked in patients with CD compared to UC and more frequent in patients who had undergone surgery. Mountfield further reported that those who were voluntarily childless were so because of the following fears:

- Fear of congenital abnormalities – 18%
- Concerns about genetic risks – 15%
- Fears about teratogenicity of IBD medication – 30%
- Medical advice about avoiding conception – 35%.

Unfortunately, ill informed counseling by doctors appeared to have been a significant factor in the wish to remain childless in 35% of respondents and this observation underlines the importance of ensuring that preconception counseling is carried out by senior specialists who can not only ensure that the correct information is imparted, but also that the same message is relayed by all who constitute the team.

Fecundity in inactive inflammatory bowel disease

Most studies show that the fertility and fecundity of patients with uncomplicated UC and CD is the same as that of the general population[19–22]. Therefore, patients with inactive uncomplicated IBD can be reassured that their chance of conceiving is the same as if they did not have the condition.

Fecundity in active inflammatory bowel disease

In contrast to those with inactive disease, patients with IBD with active disease or who have had surgery experience decreased fecundity compared to the general population, a fact which has been demonstrated in several studies[23–25]. The decrease is probably small and is seen mostly with active CD[26–28]. The most likely explanation for this situation is the intimate contact of inflamed loops of bowel with the female reproductive organs causing their inflammation. This not only results in blockage of the fallopian tubes, but may also contribute to the dyspareunia reported by some patients; it also may influence the frequency of intercourse during active disease, especially if the CD affects the perineum or pelvic structures[29].

Inflammatory bowel disease surgery and fecundity

Olsen *et al*. compared the fecundity of patients before and after restorative proctocolectomy and ileal pouch–anal anastomosis (IPAA) with the fecundity of women in the general population[24]. Whereas these investigators demonstrated a fecundity ratio of 1.0 preoperatively, following surgery it dropped dramatically to 0.2 ($p<0.001$). Based on comparative studies between IPAA and ileo–rectal anastomosis in patients with familial adenomatous polyposis, this reduction in fecundity is likely to be associated with the IPAA operation itself, because it does not appear to occur with ileo–anal anastomosis. Perhaps the pelvic dissection associated with IPAA engenders more fibrosis and inflammatory response in the adjacent upper genital tract.

The marked reduction in fecundity following IPAA represents a pivotal point in the preconception counseling of female patients with UC. Based on this finding, the European Evidence Based Consensus on the Management of Ulcerative Colitis document suggests in statement 7K that: 'in fertile female patients, the option of an ileo–rectal anastomosis should always be considered because fecundity is at risk after IPAA'[30,31].

In other words, if a patient with UC has very active colitis which warrants surgery, then rather than proceeding with IPAA which is normally considered the best operation, one could offer the patient, as a temporizing measure, an ileo–anal operation until such time that the patient completes her family, at which stage IPAA can be offered. However, as part of the counseling discussion, patients need to be made aware that because the rectum remains *in situ* following the ileo–rectal anastomosis, they will remain symptomatic. Under such circumstances, this approach is predicated on the degree of inflammation not being too severe.

An alternative that also may be offered to patients requiring surgery for active colitis is to propose a subtotal colectomy (leaving the rectum *in situ*) and formation of an ileostomy, again offering an IPAA at a later stage.

Some patients proceed with the IPAA and if they fail to conceive in the ensuing years decide to undergo *in vitro* fertilization (IVF), with the rate of IVF being greater than in the general population.

Patients with active CD also may have reduced fecundity[26,31]. This may be related not only to the disease process itself with inflammation affecting the fallopian tube, but also to the effect of previous surgery with subsequent adhesions or alteration of pelvic anatomy itself, and also factors such as pain on intercourse, which is often markedly worse during disease flare up[27]. This latter point needs to be sensitively explored in any preconceptional counseling session.

Effects of inflammatory bowel disease on the outcome of pregnancy

Most population based studies show a higher incidence of adverse outcomes for patients with IBD[28,32,33]. Cornish *et al*. carried out a large

meta-analysis to assess the risk of adverse outcomes in pregnant women with IBD[19]. The 12 studies included some 3907 patients with IBD and 320,531 controls. The analysis confirmed significant increases in adverse outcomes as follows:

- Prematurity x 1.87 (95% Cl 1.52–2.31)
- Low birth weight x 2 (95% Cl 1.38–3.19)
- Cesarean rate x 1.5 (95% Cl 1.26–1.79)
- Congenital abnormality x 2.37 (95% Cl 1.47–3.82)

Interestingly, the finding of an increase in congenital abnormalities was not present in four out of the 12 studies, but only in the later and larger studies. Further, the increase was only present in the UC subset of patients ($p<0.009$) and not found in CD ($p=0.06$). Similar findings were also noted by Mahadevan *et al*. in a population based study[34]. However, the question of whether UC was a predisposing factor for congenital abnormalities was looked at in another population based study[35]. Norgard *et al*. noted a slight increase in some forms of selected abnormalities (e.g. limb deficiencies), but overall there was no increase in congenital abnormality compared to the general population.

In general, the adverse outcomes described above have been presumed to be associated with disease activity at the time of conception[35,36]. Whilst this was not the case in the Mahadevan study, a most prudent approach suggests that it is best to try and conceive when the disease is under good control[37]. All subsequent relapses need to be treated aggressively to bring the disease back under control.

Effects of pregnancy on inflammatory bowel disease

It is impossible to predict how the pregnancy will affect underlying IBD. The relapse rate is about 33%, the same as in the non-pregnant state. Approximately one-third of patients will experience a worsening of their condition, one-third will remain the same and one-third will experience an improvement[38,39].

Effects of inflammatory bowel disease medication on conception and outcome

The effects of IBD drugs on conception and pregnancy often form the main focus of the patient's anxiety. During counseling it is important to understand the natural fears that patients have about drugs causing malformation. *It is equally important to get across the most important message that will need to be reiterated at every encounter, which is that the best outcome for the baby is for the mother to be as well as possible throughout the pregnancy and that virtually whatever is required to achieve this state must be done*. At the end of the discussion, patients must understand that it is a balance of achieving the benefit of treatment (or deterioration if the drug is withdrawn) against possible risks.

A simple and easily understandable analogy that I always use during counseling goes as follows. I describe the fetus as being akin to a space man inside a space capsule. The mother is the space capsule. The survival and well-being of the spaceman depends on the space capsule being in good working order. In the same manner, the best outcome for the fetus is for the mother to be in the very best of health that can be achieved.

Drugs and the fetus

IBD drugs that can be used pre/postconception

5-Aminosalicylic acid (mesalazine/mesalamine – FDA category B) In conventional doses, this agent is safe. Rahimi *et al*.'s meta-analysis did not reveal concerns about its use[40]. They obtained the following odds ratios (OR) for the following endpoints: congenital abnormalities

OR 1.16, stillbirths OR 2.38, spontaneous abortion OR 1.14, preterm delivery OR 1.35 and low birth weight OR 0.93. Whilst the OR was 2.38 for stillbirths, there were very wide confidence intervals (95% CI 0.85–8.72) and so it was not significant. Historical concerns about sulfsalazine have not been borne out in population based, case–controlled studies[41].

Corticosteroids (FDA category C) (prednisilone/budesonide/hydrocortisone) Steroids are commonly used in IBD in the treatment of an acute flare up and, as such, there is a pressing need to get the condition under control. It is in this context that a judgment must be made regarding their use. A prospective case–controlled study by Gur *et al*. of 311 women using systemic steroids in the first trimester concluded that glucocorticosteroids did not constitute a major teratogenic risk[42]. Additionally, this study did not find an increase in cleft palate which had been reported in other studies[41,43]. Given these data, the use of steroids in a flare up is an appropriate therapy.

Thiopurines (FDA category D) (azathioprine (AZA), mercaptopurine) Many of the data on these agents are based on their extensive use in patients with organ transplant or rheumatological conditions such as systemic lupus erythematosus (SLE). Despite the FDA classification of category D, most case studies in both the transplantation setting and the IBD literature do not show a significant increase in congenital malformation[44,45]. Based on the favorable human data, most gastroenterologists recommend the continuation of azathioprine, although it crosses into breast milk so that manufacturers caution against breastfeeding. The evidence for clinical harm, however, is poor.

Cyclosporine/ciclosporin (FDA category C) Cyclosporine can be used in severe colitis in a attempt to avert colectomy, which is associated with a high rate of fetal mortality[46]. There is no evidence that it exerts any statistically significant teratogenic effect, although some evidence suggests that it may be associated with prematurity and be more likely to cause maternal hypertension[47]. Because it crosses into milk, breastfeeding is contraindicated.

Infliximab (FDA category B) Infiximab is a monoclonal anti-tumor necrosis factor (TNF) antibody used when a patient with IBD fails to respond to other therapies. Evidence from the Infiximab Safety Database, the TREAT registry, OTIS (Organisation of Teratology Information Specialists) and the postmarketing reports collected by the manufacturer which describe several hundred patient outcomes do not provide significant evidence of teratogenicity[48,49]. In addition, Mahadevan reported a series of ten patients intentionally treated by regular infusions throughout their pregnancy which failed to show any teratogenic effects[50]. Infliximab does not cross the placenta until about week 24 of gestation.

IBD drugs which must never be used in pre/postconception

Methotrexate (FDA category X) Methotrexate is a folic acid antagonist and interferes with DNA synthesis. It is both teratogenic and acts as an abortifant[51]. Because it remains detectable in tissue for a long time, both the intended father (if he has been on it) and the woman contemplating conception must come off it 6 months before pregnancy is attempted, and reliable contraception must be used during this washout period.

Thalidomide (FDA category X) Use of this known teratogen has been limited to complex patients who failed on other treatments. Thalidomide inhibits TNF by increasing degradation of TNF mRNA. The devastating fetal effects (phocomelia) of this agent are well documented. As with methotrexate, thalidomide

should be stopped by the IBD patient (including the intended father if he is on it, see below) for at least 1 month and preferably longer before contemplating attempting to conceive and reliable contraception must be used during this washout period.

Mode of delivery

The mode of delivery should be decided by normal obstetric criteria. With quiescent or mildly active disease, vaginal delivery remains the norm. This includes patients with either an ileostomy or a colostomy (ECCO statement 11E)[52]. However, counseling should also cover special situations where a planned cesarean section should actively be discussed. The two special circumstances are active perianal CD and UC patients with IPAA.

Delivery in women with perianal Crohn's disease

In a study by Ilnyckyji *et al*., out of 54 patients with IBD who delivered vaginally, 15 had perianal CD. Of these, four had active disease and all reported a deterioration in their condition following vaginal delivery[53]. In contrast, in 11 patients with inactive CD, none reported deterioration. This finding supports the clinical practice of recommending a planned cesarean section in active perianal CD and allowing a trial of vaginal delivery in inactive CD, albeit with a low threshold for converting to cesarean section.

Delivery in women with ileal pouch–anal anastomosis

The general recommendation for IPAA patients is to have a cesarean delivery to avoid the risk of damage to the anal sphincter. Unlike other patients, the integrity of the anal sphincter is all that IPAA patients have to keep them continent. This is the reason why we normally advise delivery by cesarean in IPAA patients. Despite this clinical truism, there is little evidence to support this recommendation[54]. This dichotomy needs to be discussed with the patient at an early stage in her care, and the patient's decision should be recorded in the case notes for the obstetric care team to be aware of as the pregnancy progresses. If, after counseling, the patient still desires to attempt vaginal delivery, then the threshold to convert to cesarean should be low and no instrumentation should be attempted

Inflammatory bowel disease affecting the intended father

There is no evidence that IBD *per se* affects male fertility. However, surgery for IBD and medication used to treat the condition may have an effect on male fertility.

Surgery in the intended father Impotence, usually in the form of erectile dysfunction or retrograde ejaculation, following either proctocolectomy or IPAA surgery is a potential problem. A review of this topic by Lindsey and Mortensen quoted a risk of sexual dysfunction in the order of 1–3% after pelvic surgery, but these authors conceded that partial impotence or retrograde ejaculation may be twice as common when it is specifically sought by carefully structured questionnaire[55]. They also made the suggestion that consideration be given to offering storage of semen prior to IPAA in order to avoid this potential problem. The importance of this proposal is that if the male partner of the woman is considering pregnancy suffers with UC and is likely to require pelvic surgery in the form of a IPAA, then counseling needs to address this issue. The options are either to try to postpone the pelvic surgery until such time as conception has been achieved or, if this is not practical, to

see whether storage of semen can be arranged. Should the man be unfortunate enough to be in that small percentage in whom impotence occurs, then there remains the fall back option of using the stored semen to enable assisted conception to occur

Medication in the intended father Whilst many of the drugs used in treating IBD in the male are of no known concern with regards to preconception issues, three need special consideration, namely, sulfasalazine because of its effect on fertility and, more worryingly, methotrexate and thalidomide because of their devastating effects on the fetus.

Sulfasalazine is a folic acid antagonist which can cause a dose related decrease in sperm motility and total sperm count. There is no evidence that it is teratogenic[56,57]. This is not a problem with the other 5-aminosalicylic acids (5-ASAs). It is important to recognize that although sulfasalazine is a folic acid antagonist, these effects are not reversed by ingesting additional folic acid. On the other hand, consideration may need to be given to withdrawing the sulfasalazine in the male patient and substituting the newer 5-ASA compounds if there has been difficulty in getting the female partner pregnant.

Methotrexate is a dihydrofolate reductase inhibitor and interferes with DNA synthesis. This drug is used in patients with active or relapsing IBD, usually CD patients who are resistant or intolerant to azathioprine. Because methotrexate is both an abortificient and teratogenic, it is crucial that the male partner stops using it at least 6 months before contemplating attempting to inseminate his partner and two reliable forms of contraception continue to be used during this 'washout period'.

Thalidomide is an anti-TNF inhibitor used in only a very small number of patients who have failed on to respond thiopurines or methotrexate. Because of its well known and devastating teratogenic effects (phocomelia) it is essential that exactly the same precautions need to be undertaken as with methotrexate.

Because both methotrexate and thalidomide are only used in IBD patients who have had difficult or resistant IBD, a very careful consultation with the intended father's gastroenterologist needs to be undertaken because of the consequences of embarking on this course of action.

CONCLUSION

Preconceptional counseling of the patient with IBD needs to be accomplished by an experienced specialist in order to provide consistent evidence-based advice. Such advice must be sensitive, tailored to the individual circumstances and disease type, and balanced in all regards. The aims are multiple:

1. If at all possible, to conceive when the disease is under control;
2. Regardless of the degree of activity, all efforts need to be made to keep the disease under control;
3. All flare ups should be treated very actively. The majority of IBD medications used are safe in pregnancy.

The analogy of the fetus being like a spaceman inside the mother ship must be introduced from the start to underline that fact that a successful outcome depends on the mother being kept well and in a good state of health.

Finally, although there is a slight increase in adverse pregnancy outcomes in patients with IBD, the majority will, with good care, deliver healthy babies.

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11
Neurological disorders in pregnancy

Dominic Heaney

INTRODUCTION

Neurological disorders are a significant cause of morbidity and mortality in pregnancy. In the UK between 2003 and 2005, women with neurological conditions accounted for 37 out of a total 87 'indirect' maternal deaths (those not arising from pregnancy or birth), with stroke (n = 24) and epilepsy (n =11)[1] accounting for the majority of deaths from neurological causes[2].

Neurological assessment can distinguish between neurological symptoms that are common in pregnancy (such as dizziness, pain and urinary frequency) and those that might indicate a more significant disorder. Neurological conditions can arise from 'organic' disorders, which are usually associated with clear-cut abnormalities with neurological investigations, but may also result from less well understood 'functional' problems, typically causing pain, fatigue or even alteration in levels of consciousness. All neurological conditions may present both medical and obstetric challenges to clinicians unfamiliar with their management within the context of pregnancy.

Fortunately, the natural history of key neurological conditions has been observed during pregnancy, providing a useful basis on which to counsel women and organize services. Less information is available about the safety of neurological treatments or investigations during pregnancy or obstetric and neonatal outcomes for these women. Therefore, many decisions rely on applying key obstetric and neurological principles to situations where published data are not available.

This chapter outlines neurological assessment and investigation in pregnancy before considering the most common and important neurological presentations – multiple sclerosis, stroke, epilepsy and pain. These conditions arise from different pathologies, but their management allows the basic principles of management of other neurological conditions to be described. Overall women with pre-existing neurological conditions, or women who present with neurological symptoms during pregnancy rely on good communication between their obstetrician, neurologist, physician, neonatologist and anesthetist to achieve optimal obstetric and neonatal outcomes.

NEUROLOGICAL ASSESSMENT (CLINICAL EXAMINATION AND INVESTIGATIONS)

Neurological assessment in pregnancy is undertaken in the usual way with clinical history and examination guiding use of investigations.

Even when a number of neurological symptoms may be attributed to pregnancy, as when considering neurological symptoms in the non-pregnant woman, much can be established by careful emphasis on the onset, progression and associated features.

Neurological examination should consider higher mental function, cranial nerves and

neurological assessment of the trunk and limbs. In later pregnancy, small mechanical changes in gait and ability to participate in tests of hip power may be noted, but, in general, changes in the key markers of tone, power, co-ordination, sensation or reflexes should not be attributed to pregnancy itself. Similarly, inspection should not reveal any changes in muscle bulk or symmetry.

Neurological investigation may cause more concern in pregnancy, although in most cases anxieties are unfounded and tests may be undertaken as in the non-pregnant woman.

For example, neurophysiologic assessment such as electroencephalography (EEG), nerve conduction studies and electromyography (EMG) may be uncomfortable but are non-invasive and safe.

Cerebrospinal fluid is obtained by the standard method of lumbar puncture, although access may be difficult in later pregnancy and should be undertaken by suitably skilled practitioners. Spinal fluid can show evidence of a wide range of central nervous system disorders including infection, inflammation, demyelination or, with cytological analysis, presence of neoplasia. Lumbar puncture is relatively invasive and standard relative and absolute contraindications should be considered. In particular, consideration of any coagulation disorders should be made, and lumbar puncture should not be undertaken in suspected raised intracranial pressure, as brain stem herniation may occur. If there is any doubt, clotting studies and neuroimaging should precede this investigation.

Neuroimaging is often an integral part of patient assessment. The ionizing radiation associated with computerized tomography (CT) neuroimaging leads to obvious concern on the parts of both clinicians and patients when imaging the pregnant woman. Nevertheless, CT of the head involves a fetal radiation dose exposure of less than 0.0005 rad and the impact of fetal exposure is likely to be small[3]. Uterine shields are routinely employed and reduce fetal exposure further. In some cases the advantages that CT imaging of the head offers – it can usually be obtained promptly and interpreted with ease – particularly when cerebral hemorrhage is suspected – may outweigh any putative risk of exposure to ionizing radiation to mother and fetus.

Nevertheless, in most cases magnetic resonance imaging (MRI) offers greater resolution and extent than CT and therefore is likely to be more clinically valuable. It does not involve ionizing radiation and thus avoids any issues related to fetal radiation exposure in pregnancy. However, although there is no evidence of fetal harm in humans after 20 years of widespread use of this technology many guidelines recommend that, when possible, MRI be delayed until the end of the first trimester and particularly when high-field (3 Telsa) magnets are proposed. However, even in the first trimester, the advantages may on occasion outweigh any theoretical risks.

It should be noted that in contrast to CT, which may be acquired in a few minutes, MR images are significantly more time-consuming to obtain. Depending on the technology being used, MR scanning of more than two areas of the neuroaxis (for example, head and cervical spine) may take in excess of 60 minutes. This may not be appropriate when an individual's condition is unstable, or the woman is confused.

In later pregnancy, even with shorter duration MRI, women may have difficulty lying supine as compression of the inferior vena cava by the gravid uterus impairs venous return, leading to hypotension and ultimately fetal hypoxia. MR radiographers will be familiar with methods by which this can be overcome, such as use of a lateral wedge or tilt. The size of a heavily pregnant woman may occasionally preclude the use of some CT or MRI scanners and claustrophobia may be more of an issue than usual.

Iodinated contrast agents can be used in pregnancy and lactation but the intravenous contrast agents used in MR (e.g. gadolinium) should not[4].

Certain clinical situations may indicate the use of other ionizing radiological techniques such as digital subtraction angiography – typically used to visualize the intracranial cerebral vessels or spinal vessels in suspected vascular malformations such as aneurysms or arteriovenous malformations. The expected radiation dose depends on the procedure. For example, this may be low with head imaging, but higher for spinal procedures. Clinicians should balance the risks of not fully investigating a patient against potential harm to the fetus.

NEUROLOGICAL CONDITIONS: EPIDEMIOLOGY AND DEMOGRAPHY

In many cases, women with neurological disorders are aware of their condition before conception. But neurological illness may change or even present for the first time during pregnancy, presenting a very wide range of clinical and obstetric challenges to those involved in their care.

Nevertheless, it is self-evident that the majority of neurological conditions seen by obstetric services reflect those disorders that typically present among women of childbearing age. Thus obstetric-neurology clinics or other forms of neurology-obstetric liaison services will be dominated by the four disparate conditions of multiple sclerosis, stroke, epilepsy and pain syndromes – typically headache. Consequently, this chapter focuses on these four disorders. Nevertheless, the descriptions of the neurological impairments that arise in these conditions and their management can be applied to other rarer conditions. It is very unusual for women with neurodegenerative conditions such as Parkinson's disease or dementia to be pregnant, and these disorders are mentioned only in passing.

MULTIPLE SCLEROSIS

Definition and incidence

Multiple sclerosis (MS) is a disease of the central nervous system (brain and spinal cord) that is characterized by both neuroinflammation and neurodegeneration. Incidence is 3.6 cases per 100,000 person years (95% CI 3.0–4.2) in women and is higher in northern latitudes, although this trend seems to be reducing[5]. The disease can have many clinical manifestations (with sensory loss in the limbs, visual loss, subacute motor loss, double vision and gait disturbance being most common) and a highly variable pace of progression (relapsing remitting, secondary progressive, primary progressive and progressive relapsing). The median survival from onset of symptoms is 38 years. MS is usually diagnosed between 20 and 50 years old, and so women with MS will therefore become pregnant relatively early in the course of their illness and usually have correspondingly little associated disability. Nevertheless the issues of symptom management and counseling are relevant at all stages throughout pregnancy.

Preconception

Preconceptional counseling offers the opportunity to discuss the potential effect that pregnancy may have on MS, the effect that MS-related neurological impairment may have on pregnancy and delivery, and the use of disease modifying or symptomatic treatments in both pregnancy and postpartum.

Many people with relapsing and remitting MS are treated with disease modifying drugs (DMDs). These include beta-interferons and a synthetic polypeptide, glatiramer acetate. These treatments are administered by subcutaneous or intramuscular injection at least twice weekly and have been shown to have a modest but significant effect on reducing

relapse rate (approximately 30% per year) and to some extent long-term disability.

The safety of these treatments in pregnancy has not been established. The US Food and Drug Administration (FDA) have assigned glatiramer acetate to pregnancy safety category B (i.e. appears to be safe for pregnancy in animal studies but not adequately studied in pregnant humans)[6]. It has not been shown to be a teratogen in animal studies and its large molecular weight (4700–11,000) suggests that if its crosses the placenta, it does not do so by simple diffusion. The interferons are US FDA pregnancy safety category C (i.e. human studies are lacking and animal studies are either positive for fetal risk or lacking as well). In high doses, interferons appear to be abortifacients, but not teratogens.

Current advice is that in most cases women should stop treatment with DMDs if they are planning to become pregnant – or find themselves unexpectedly pregnant. Although stopping treatment may expose the pregnant woman to increased risk of relapse, in absolute terms the risk is relatively low (an 'extra' 0.2 relapse/year)[7]. This risk is further modified by the beneficial effect of pregnancy itself (see below). It should be noted that some experts would offer women with MS the option of continuing agents for which there are limited reassuring pregnancy data, such as glatiramer acetate.

Women with MS may also be taking other drugs, such as antimuscarinics for bladder disorders (e.g. oxybutinin), antispasmodics (e.g. baclofen or diazepam) and antidepressants (e.g. tricyclic antidepressants). Antimuscarinics, benzodiazepines or tricyclic antidepressants have low teratogenic potential.

Rarely, patients with MS or other conditions that cause spasticity have implantable devices delivering an antispasmodic agent, typically baclofen, intrathecally. These pumps are sited extraperitoneally within the abdominal wall. Although the local infusion of baclofen intrathecally presents a significant theoretical advantage in terms of significantly reduced serum levels (and therefore transplacental transfer) of drug compared with oral treatment, there are practical concerns regarding 'kinking' and blockage of treatment catheters. Nevertheless, case reports have reported successful obstetric outcome[8].

Genetics of multiple sclerosis

The inheritance of MS is poorly understood and is likely to involve a complex interaction between genetic and environmental factors. Nevertheless, in general, the child of a mother with MS has an approximately 2–3% chance of developing MS, compared with 0.1% prevalence in the general population[9], although the mother should be counseled that should MS occur, symptoms are unlikely to present until the third decade or later. The risk is increased further if both parents are affected.

Effect of pregnancy on relapse rate

Women with MS who are considering pregnancy will seek to establish whether pregnancy will affect the number of relapses they suffer and the overall course of their condition. In the past, the relatively high number of relapses observed postpartum led to the false conclusion that pregnancy might lead to a long-term poorer outcome when compared with non-pregnant women who have not been pregnant. More reassuring evidence has been obtained from a large, prospective study ('PRegnancy In MS'/PRIMS), which has continued to monitor enroled mothers many years after enrolment into the study[10]. This study showed that, although risk of relapse postpartum was increased by a factor of two for approximately 3 months' postpartum, this was equally balanced by the observation of significantly fewer relapses during pregnancy. Thus, overall no difference is observed in the long-term number of relapses and disability of women who become pregnant.

Relapse management

Although the risk of relapse is reduced during pregnancy, this 'protective' effect is less pronounced during the first and second trimesters. Should relapse occur, management is the same as for non-pregnant women. Mild relapses require no treatment, but are likely to warrant assessment by occupational or physiotherapists – as levels of disability may be increased for several weeks. High-dose corticosteroids (for example a total of 1 g of methyl-prednisolone administered intravenously or orally for 3–5 days) may be used to speed up remission. Steroids present well known risks including reduced bone density, infection, mood alteration and adverse gastrointestinal effects. Nevertheless, where standard precautions and pretreatment assessment are applied, steroids may avoid the need for hospitalization or reduce considerably the length of stay.

Occasionally, relapses are severe and progressive. In the non-pregnant woman these may be managed with more aggressive treatment, such as mitoxantrone (a chemotherapeutic agent) or natalizamub (a monoclonal antibody, which reduces white cell traffic into the CNS). These treatments are either clearly teratogenic and embryotoxic or have no evidence to support their safety in pregnancy. Their use should consider the advantages and risks to both mother and fetus on a case-by-case basis, taking into account the mother's condition and the gestation. Intravenous immunoglobulin (IVIG)[11] or possibly hemodialysis may pose less risk to the fetus, but there is less evidence to support their efficacy in reducing MS progression.

Management of other symptoms

Women with MS may suffer from a range of symptoms during pregnancy including fatigue, restless lower limbs and urinary symptoms.

Non-pharmacological advice to improve quality of sleep ('sleep hygiene') should be offered. These include examination of an individual's sleep routine and the sleeping environment. Women should be encouraged to avoid psychologically stimulating activities in the evenings and intake of pharmacological stimulants such as caffeine should be minimized. Drug treatments such as amantadine or modafanil, which are sometimes used to reduce MS-related fatigue, cannot be recommended, as there is no evidence to support their safety in pregnancy.

A sense of restlessness in the lower limbs is common in pregnant women, but women with MS may also have a degree of spasticity manifest as painful or irritating spasm. Neurological examination can be useful to demonstrate spasticity and localize relevant muscle groups. Physiotherapy advice and possibly use of benzodiazepines, which are regarded to be relatively safe in pregnancy may be warranted.

Urinary symptoms should be carefully evaluated as impaired bladder emptying in women with MS predisposes to infection. Baclofen to treat bladder spasm is a reasonable option in pregnancy. Women with pre-existing urinary problems may be concerned that vaginal delivery will exacerbate urinary symptoms postpartum, and this may be a matter of understandable concern to the individual. In such cases, individualized advice should be given.

Immobility in pregnancy increases the risk of thromboembolism, so there should be a low threshold for the use of thromboprophylactic measures, such as graduated compression stockings or low molecular weight heparin in women with impaired mobility due to MS.

Third trimester and delivery

In most cases, the third trimester and the peripartum period are not different between women with MS and the non-MS population. Specifically, obstetric and neonatal outcomes

do not differ – with similar rates of induction, instrumentation, cesarean section and infant mortality.

Nevertheless, women with MS may have specific neurological impairments that affect interpretation of symptoms during pregnancy. For example, women with plaques at T11 or lower will have impaired bladder and bowel function but normal sensation of uterine contractions and pain. Lesions between T6 and T10 will impair perception of uterine contractions and where significant lesions are present above T6, other signs of labor will have to be considered, such as worsening lower limb spasticity.

Urinary retention can occur during labor or postpartum, particularly when epidural analgesia is used; consideration should be given to the use of an in-dwelling urinary catheter from early in the labor until after delivery (when the woman is mobile and the effects of any epidural have worn off) in women with impaired bladder function. Difficult (and in particular instrumental) vaginal delivery may exacerbate urinary incontinence, and so should be avoided if this is a pre-existing problem.

In the past there have been theoretical concerns expressed regarding the safety of epidural anesthesia, and exacerbation of MS. Evidence from the PRIMS study, however, has been reassuring, demonstrating no significant difference in outcomes between women with and without epidural anesthesia[12].

Postpartum

Women who are more mildly affected by MS are more likely to choose to breastfeed. Although there are small studies suggesting otherwise, the general consensus is that breastfeeding does not protect against (or cause) a postpartum relapse[13]. Women who have been taking DMDs before pregnancy balance the benefits of breastfeeding against the risk of relapse without treatment. Women who defer DMD treatment should be counseled that should they suffer relapse, most centers require good recovery before DMD is restarted and so further delay may occur.

A small number of centers have advocated prophylactic use of IVIG postpartum to prevent relapses[14]. Activity of disease in the year prepregnancy and in the first trimester to some extent predicts the risk of relapse in the 3 months' postpartum. Nevertheless, a recent authoritative multivariate model predicts that using this information to make a decision about treatment would lead to 50% of women being treated unnecessarily[13]. IVIG is expensive and is derived from pooled human serum, which presents theoretical risks of infection. Thus, the current consensus is not to treat prophylactically.

STROKE

Definition and incidence

Stroke is an acute neurological impairment that follows interruption of blood supply to a specific part of the brain. Blood supply may be interrupted by thrombosis (either arterial or venous) or embolism, or in a smaller proportion of women by hemorrhage. As previously described, it is the main cause of neurological mortality in pregnancy, and represents a significant proportion of all indirect maternal deaths.

Stroke is an uncommon but serious complication of pregnancy. The incidence of stroke in non-pregnant women aged 15–44 years has been reported to be as low as 10.7 per 100,000 woman-years[15]. Multicenter or long-term observational studies are therefore required to establish the incidence in pregnancy. Estimates using such methods produce widely differing rates between 4.3 and 210 strokes per 100,000 deliveries depending on inclusion criteria with most studies suggesting an increased risk of stroke associated with pregnancy[16–18]. Most

(up to 90%) strokes in these studies occurred peripartum and up to a few weeks after the birth.

Risk factors for stroke

Physiological risk factors

Progressive physiological changes occurring throughout pregnancy predispose to stroke including increasing hypercoagulability, venous stasis and vascular wall changes. Pushing in the active phase of the second stage of labor involves episodes of significantly increased intrathoracic pressure (Valsalva) and elevation of cerebral perfusion pressure, which may lead to changes in cerebral blood flow – particularly where cerebral autoregulation or anatomy is disordered[19].

Obstetric risk factors

The main obstetric factor associated with an increased risk of stroke is pre-eclampsia and eclampsia, in particular uncontrolled systolic hypertension. This is still the major cause of death due to pre-eclampsia in the UK[1]. Age more than 35 years, black ethnicity, greater parity and multiple gestation are all risk factors for stroke, although quantifying this risk is not possible from available data.

Co-morbidity risk factors

Women who become pregnant may have co-morbidity that increases the risk of vascular events including stroke; such factors include obesity (BMI >30 kg/m^2), diabetes, pre-existing hypertension, renal and heart disease, vasculopathies such as sickle cell disease, vasculitis and collagen or atherosclerotic disease. Alcohol, tobacco and cocaine use may cause a vasculopathy or hypertension.

Migraine with aura (see later) also produces excess risk for stroke, but this condition is common and stroke in pregnancy is rare, so caution should be used when counseling women about this risk factor.

Previous stroke during pregnancy presents a particular dilemma for women considering further pregnancy. Unfortunately, few data are available, although in a follow-up study 13 of 489 (2.7%) women aged 15–40 who had suffered a stroke had a recurrent event, but only two of these occurred during pregnancy[20]. Full ascertainment of vascular risk factors, including CT or MR angiography prior to pregnancy, is appropriate to best inform the individual of her likely risk of pregnancy related recurrent stroke.

Clinical presentation and management of stroke

Presentation and investigation

Stroke presents as in the non-pregnant woman and clinical features may suggest either infarction or hemorrhage, but neuroimaging is required to confirm the diagnosis. The possibility of stroke should be considered in any woman who presents with any of the symptoms listed in Table 1. While in an imperfect screen with a specificity of 88% and a sensitivity varying from 66 to 100%, the Cincinnati Prehospital Stroke Scale may be a useful screening scale to help guide whether an obstetric patient presenting with headache or other softer neurologic complaints warrants prompt complete neurologic assessment and neuroimaging. This screening scale is summarized in Table 2.

If any of the three elements in the scale or any other neurologic findings are newly abnormal, the possibility of acute stroke is high and the patient should have urgent imaging and evaluation by a neurologist.

Table 1 Symptoms that warrant consideration of stroke

Sudden weakness or numbness of face, arm or leg, especially if on one side of the body
Sudden confusion
Trouble speaking or understanding
Sudden trouble seeing in one or both eyes without a prior history of migraines
Sudden trouble walking
Sudden loss of balance or coordination not readily attributable to pregnancy
Sudden severe headache with no known cause

Table 2 Cincinnati Stroke Scale

Three elements

1. Facial droop
   a. Have the patient smile and assess for facial droop
      i. Normal: both sides of face move equally
      ii. Abnormal: one side of face does not move
2. Arm drift
   a. Have the patient hold both arms out and up with palms facing upwards
      i. Normal: both arms move equally
      ii. Abnormal: one arm drifts compared with the other
3. Speech
   a. Have the patient repeat a sentence
      i. Normal: patient uses correct words with no slurring
      ii. Abnormal: slurred or inappropriate words or mute

As stated above, most pregnancy related cerebral infarction occurs around the time of delivery and early puerperium[16,21,22] at a time when the mother is often bed bound, still hypercoagulable and may just have had pelvic surgery, i.e. cesarean section or instrumental vaginal delivery. Widespread adoption of postpartum thromboprophylaxis use in the UK has been associated with a decrease in the incidence of cerebral infarction due to emboli, but not that due to uncontrolled systolic hypertension[1].

Stroke is a medical emergency. Patients with acute arterial ischemic stroke from embolism or thrombosis can have their long-term outcome greatly improved by the use of thrombolytic therapy within 180 minutes of the onset of symptoms. Therefore all patients with symptoms suggestive of stroke require prompt neuroimaging to determine whether they have had an ischemic stroke that may benefit from the use of thrombolytic therapy. Table 3 lists the recommended guidelines for timing of interventions for patients presenting with acute ischemic stroke. Table 4 reviews the other assessments recommended for patients presenting with possible acute stroke. Patients should be positioned with the head of the bed lowered between 0 and 15 degrees and, if blood pressure is greater than 180/105 mmHg, it should be treated acutely with intravenous labetalol. Aspirin should not be given while investigating an acute stroke. Table 5 reviews

Table 3 Patients presenting with symptoms of acute stroke to an emergency room should

Be seen by a provider within 10 min with early notification of local 'stroke team' of possible stroke patient
Have a neurologic assessment and head CT performed within 25 min of presentation
Have the head CT scan read with determination of whether they are candidates for fibrinolytic therapy within 45 min of presentation
Receive fibrinolytic therapy within 60 min of presentation to the A&E and no longer than 180 min since the time of onset of symptoms

Table 4 Additional investigations for patients presenting with possible acute stroke

Assess airway (can the patient protect her own airway or does she require intubation), breathing (what is her respiratory rate and oxygenation) and circulation (are her pulse and blood pressure normal)
Obtain secure intravenous access
Obtain a fingerstick glucose measurement
Obtain a full blood count, urea and electrolytes, liver function tests serum glucose, serum troponin
Consider urine toxicology screen and blood alcohol level
Arterial blood gas if oxygen saturation abnormal
Obtain an ECG

the contraindications for thrombolytic therapy. The use of thrombolysis should be considered for pregnant and postpartum women with severe acute cerebral non-hemorrhagic infarction if it can administered within 180 minutes of onset of the neurologic deficit[23]. Thrombolysis is well tolerated by the fetus in pregnancy and does not seem to increase the risk of placental abruption, so should not be withheld if the maternal condition is life-threatening. Postpartum, thrombolytic therapy carries a risk of uterine or pelvic hemorrhage. However, this risk decreases with increasing time after delivery and, in most cases, the benefits of thrombolysis will outweigh the risks. Local hemorrhage can usually be dealt with by local hemostatic measures (such as uterine balloon) or surgery. Close liaison between neurologist, obstetrician and physician is essential in such cases.

It is not recommended to use thrombolytics for acute ischemic stroke in the setting or probable or confirmed pre-eclampsia.

Specific syndromes are considered below, but in most cases pregnant women who have cerebral infarction should be managed within a multidisciplinary stroke unit. Low dose aspirin is the mainstay of treatment for acute ischemic stroke. Aspirin and the other antiplatelet agents (aspirin with dipyridamole, or clopidogrel) are also the most effective preventive treatment of stroke. Unfractionated or low-molecular weight heparin is not recommended for acute stroke or stroke prevention except in the case of stroke from cardioembolism, arterial dissection or large artery intraluminal thrombus. Warfarin is teratogenic and usually avoided in pregnancy.

The differential diagnosis of acute stroke in pregnancy is broad and includes migraine, transient ischemic attacks, head trauma, brain tumor, Todd's palsy (a neurologic deficit

Table 5 Contraindications and cautions to thrombolytic therapy for acute stroke

Contraindications
Intracranial bleed on CT
Presentation suggests SAH
Multilobar infarction on CT
History of intracranial hemorrhage
Uncontrolled hypertension (>185/110 mmHg when treatment fibrinolytics to be given)
Known AVM/neoplasm
Witnessed seizure at onset of stroke
Active bleeding/acute bleeding diathesis (platelets <100, PTT elevated, INR >1.7)
Within 3 months of intracranial or intraspinal surgery/serious head trauma or previous stroke
Arterial puncture at a non-compressible site in the past 7 days
Cautions
Consider whether benefits of thrombolytic therapy outweigh risks
Minor or clearing stroke
Within 14 days of major surgery or trauma
Within 21 days of GI/GU hemorrhage
Within 3 months of acute MI
Post MI pericarditis
Glucose <50 or >400 mg/dl

SAH, subarachnoid hemorrhage; AVM, arteriovenous malformation; PPT, partial prothrombin time; INR, international normalized ratio; GI, gastrointestinal; GU, gastric ulcer; MI, myocardial infarction

following a seizure), systemic infection, functional deficits ('conversion disorders') and toxic metabolic disturbances (e.g. hypoglycemia, acute renal failure, hepatic insufficiency, drug intoxication). Perhaps the most challenging and common differential diagnosis for stroke in the obstetric population is migrainous aura. Migrainous auras are typically brief and more likely to be positive (the alteration of a sensory perception) rather than negative (the absence of a perception), e.g. wavy lines in vision versus no vision or 'pins and needles' versus numbness. Migrainous auras are most commonly visual (typically scotoma and/or zig-zag lines) or sensory ('pins and needles') in the perioral region. Less commonly, they are sensory in the upper limbs or difficulties with speech (typically disarticulation with word finding difficulty or use of wrong words but no difficulty with comprehension). Neurologic symptoms other than this should not be casually attributed to migrainous aura. Visual or sensory symptoms should be one sided, gradually progress and last between 5 and 60 minutes. If more than one aura symptom is present, symptoms should occur in succession rather than simultaneously. Importantly, migraine and migrainous aura is by definition

a recurring problem and the diagnosis cannot be made on first presentation of symptoms. If there is doubt about whether a patient's symptoms represent stroke/transient ischemic attack or migrainous aura, an evaluation by a neurologist and neuroimaging is advisable.

Specific stroke syndromes and their management

Pre-eclampsia and eclampsia

Presentation Pre-eclampsia is a multisystem disorder affecting 3–5% of pregnancies[24]. Although only a tiny proportion of those affected by pre-eclampsia suffer from stroke, up to 45% of women who have pregnancy-related stroke have pre-eclampsia or eclampsia[16,25]. Uncontrolled systolic hypertension and endothelial dysfunction may lead to hemorrhage or infarction[26]. Disordered cerebral autoregulation may also play a role, especially postpartum.

Investigation and management Investigation and management of pre-eclampsia will be familiar to the obstetrician and is reviewed elsewhere. Most cases of stroke in the setting of pre-eclampsia are due to arterial hemorrhage (when thrombolytic therapy is contraindicated) but cases of acute arterial thrombosis also occur. While pre-eclamptic stroke is most likely in the setting of severe hypertension (>180/110 mmHg), it can occur at blood pressures much lower than this and the acute change in blood pressure may be as important a factor as the absolute pressure. The only definitive treatment for pre-eclampsia is delivery of the fetus and placenta. Prompt neuroimaging should occur in pre-eclamptic women with sudden onset (thunderclap) headache and/or any persistent neurologic deficit. Neurosurgical consultation should be urgently sought if intracerebral blood is found on CT or MRI to guide the need for interventions to decrease intracranial pressure. Blood pressure is typically brought to a level of 160/90 mmHg (a mean arterial pressure of 110 mmHg) and not much lower as some degree of hypertension may be needed to maintain cerebral perfusion and prevent ischemia. The presence of an intracerebral bleed will complicate options for obstetric anesthesia and an obstetric anesthetist should be involved early in these cases.

Reversible cerebral vasoconstriction syndrome

Presentation Reversible cerebral vasoconstriction syndrome (RCVS) is an underrecognized and often misdiagnosed syndrome characterized by a sudden-onset, severe headache seen in association with a neurologic deficit. It is caused by reversible vascular narrowing involving the circle of Willis and its immediate branches. RCVS can present in conjunction with hypertensive encephalopathy, pre-eclampsia and reversible posterior leukoencephalopathy, physical exertion or bathing and it can occur in isolation[27]. Women may have had an uncomplicated pregnancy and present a few days after delivery with headache, cerebral irritation and neurological deficit. Investigations demonstrate infarction and/or hemorrhage.

The differential diagnosis includes subarachnoid hemorrhage, migraine, arterial dissection, vasculitis or infection.

Investigation and treatment CT, MR or catheter angiography may demonstrate multifocal segmental narrowing of the cerebral vessels, which resolves within 4–6 weeks. Spinal fluid should be normal, and this distinguishes this syndrome from subarachnoid hemorrhage (SAH).

Treatment is supportive, although vasodilators and steroids have been used.

Intracranial hemorrhage

Presentation Most intracranial hemorrhage occurring during an otherwise normal pregnancy is the result of aneurysmal SAH and arteriovenous malformation (AVM). Intracranial arterial dissection is a much rarer etiology. Hypertension, smoking, alcohol and family history are all risk factors. The incidence of SAH from aneurysmal rupture is 3–11 per 100,000 pregnancies[16], but 50% of all aneurysmal rupture in women below 40 occurs in the context of pregnancy[28]. Cavernoma and other venous anomalies are a very infrequent cause of hemorrhagic stroke.

Presentation of intracranial hemorrhage is the same as in the non-pregnant woman. Symptoms are dominated by the sudden onset of headache, often described as 'the worst headache of my life'; this presentation should always prompt consideration of the diagnosis of SAH. Meningeal irritation (due to blood spreading through the cerebrospinal fluid), altered consciousness, collapse or vomiting at onset, and the absence of lateralizing neurologic findings are features that are characteristic of SAH but not universal.

Investigation and management CT scan is very sensitive for SAH in the first 12 hours after the event, but is less sensitive with smaller bleeds and as the days go by after the initial event. Lumbar puncture is recommended in patients with a history suggestive of SAH who have a normal CT scan, especially if more than a day has passed since the onset of their symptoms. The presence of xanthochromia on cerebrospinal fluid is highly suggestive of a SAH but will not be present until 2–6 hours after the acute event.

CT offers advantages compared with MR in ease of obtaining a study and in the past was viewed as better than MRI at identifying early hemorrhage. However, the use of FLAIR and T2 sequences with MRI may be as good or better than CT at identifying an early SAH, and is better than CT at identifying a SAH in the days following the acute event.

Ruptured aneurysmal SAH may be complicated by rebleeding – with an associated mortality rate of 50–70%[29], so monitoring and management of such patients should take high priority. Four per cent of patients will rebleed within 24 hours of the initial bleed, and up to 20% within the first month. Vasospasm, cerebral infarction, hydrocephalus, increased intracranial pressure, seizures and hyponatremia are other possible complications. Medical treatment usually involves intravenous fluids, bed rest, compression stockings, analgesia, laxatives and nimodipine 60 mg 4-hourly[30]. Medical management of SAH should be undertaken at or in close liaison with a neurosurgical center.

Once the diagnosis is established, the etiology for the SAH must be determined with cerebral angiography, CT angiography or MR angiography. While cerebral angiography remains the most sensitive test, it is rapidly being replaced by CT angiography due to the ease of testing and steadily improving technology. All of these tests can be safely performed in pregnant or postpartum women when necessary (see earlier discussion).

Definitive treatment usually involves endovascular coiling or surgical clipping and the timing of these interventions will be decided by the neurosurgeon. In most cases, treatment of the mother is the primary concern, although near to or during labor, in some cases the baby may be delivered first[28,31–33]. Outside pregnancy, coiling is felt to produce better overall outcomes than clipping[34]. In pregnancy, the risks of periprocedure use of radiation, postprocedure anticoagulation and postcoiling rupture in remaining aneurysm tissue are generally outweighed by the benefit of effective treatment. At the time of SAH, women with aneurysms may temporarily lack capacity to consider these issues, but in any case, detailed discussion between the obstetrician,

the neurosurgical team and the family should take place whenever possible.

Women who have had a previous aneurysm completely obliterated by clipping or coiling may consider vaginal delivery[35]. Use of epidural anesthesia is advised. Some recommend avoidance of spinal anesthesia in women in whom the aneurysm is not totally obliterated[36], based on the hypothesis that the decrease in intracranial pressure caused by dural tap could cause an increase in transmural pressure across the arterial wall, thus facilitating rupture of a potential vascular malformation; however, anesthetic input is required as this fall in pressure is likely to be preventable.

Treatment of unruptured aneurysm

In general, management of unruptured aneurysms should be the same as in the non-pregnant state, and guided by ISUIA (the International Study on Unruptured Intracranial Aneurysms)[37]. Although rupture of aneurysm is associated with significant mortality, treatment of aneurysms also carries risk. ISUIA data suggest that the risk of treating certain low-risk aneurysms (small (<7 mm), asymptomatic, stable, anterior artery aneurysms) may be greater than the risk of conservative 'watching and waiting'. In common with many trials, pregnancy has not been specifically considered. After discussion with the woman, it may be felt appropriate to treat such aneurysms prior to conception or during pregnancy. While there are no data to guide management of women with untreated aneurysms in labor and at delivery, most clinicians would recommend early good pain control, ensuring blood pressure remains less than 140/90 mmHg and limiting the active phase of the second stage of labor. An untreated aneurysm is not, however, viewed as an indication for cesarean delivery.

Unruptured arteriovenous malformation

Presentation Arteriovenous malformations (AVM) are less common than arterial aneurysms but present similarly with acute SAH. Unruptured AVMs present a lower bleeding risk than aneurysms, and the overall risk of primary hemorrhage occurring during pregnancy is 3.5%, which is similar to the normal population[38]. Individual case reports suggest that pregnancy is not associated with significant changes to AVM[39], although the obstetrician or neurologist should emphasize the paucity of data to guide decisions in this area.

Treatment AVMs are treated with combinations of surgery, endovascular embolization and stereotactic radiosurgery. The decision about treatment is guided by a number of factors including the site and complexity of the lesion.

In most cases, AVMs are managed outside pregnancy. Although there is concern that untreated or partially treated AVMs may be at risk of hemorrhage from the hemodynamic changes of labor, the observed risk of hemorrhage is recognized to be low – particularly when epidural analgesia is used and pushing in the second stage is limited, with early resort to instrumental delivery[40,41].

Cerebral venous thrombosis

Presentation Cerebral venous thrombosis (CVT) may account for approximately 20% of strokes during pregnancy[22] and should be considered in any pregnant woman complaining of headache and drowsiness – particularly if focal neurological signs or seizures are evident. Its occurrence is now increasingly recognized with the more widespread use of MRI; the incidence in pregnancy is estimated at 11.6 per 100,000 deliveries in the US. Thrombosis of cerebral veins or dural sinuses causes injury to tissue through increased venous pressures

and (in the case of dural sinus thrombosis) decreased CSF reabsorption and increased intracranial pressure. The presentation is highly variable and may include headache with or without vomiting, focal deficits, seizures and/or mental status changes. Headache is the most common presentation with gradual onset and often localized.

Investigation and management The presence of papilloedema is not a sensitive or specific sign of CVT and diagnosis relies on neuroimaging, which will demonstrate venous distribution infarction with possible hemorrhage. MRI in combination with MR venography is the best test for diagnosing CVT. CT scans can be normal in up to 30% of cases.

Even when hemorrhage is evident on imaging, CVT is treated by anticoagulation for 6–12 months. During pregnancy, therapeutic doses of low molecular weight heparin may be used, although evidence for its benefit is lacking. Data from non-pregnant patients suggest that 80% have complete recovery and that the rate of recurrence is well below 10%.

Paradoxical embolism

Patent foramen ovale (PFO) is an interatrial communication present in approximately 27% of adults, but in up to 50% of young patients presenting with stroke[42]. This abnormal communication may allow right-to-left shunting of venous emboli directly into the arterial circulation, or provide a focus of thrombus formation. While case–control studies consistently show a relationship between stroke and PFO, prospective data show that a PFO is not associated with an increased risk of first or recurrent stroke. While there is still controversy over this issue, most experts would currently recommend that patients with a single prior stroke, a PFO and no other thrombotic risks should receive only the usual stroke prevention treatments, i.e. antiplatelet agents such as acetylsalicylic acid (ASA). Patients with a PFO (regardless of whether they have had a stroke) should therefore receive anticoagulation with warfarin or heparin only if they have another indication for anticoagulation. Decisions about the management of patients with recurrent stroke and PFO, or those with a PFO with a single stroke but multiple risk factors for recurrence (thrombophilia, atrial septal aneurysms) should be made in collaboration with a cardiologist, hematologist and (when pregnant or considering pregnancy) a high risk obstetrician and obstetric physician. Options to be discussed include full anticoagulation or surgical closure of the PFO prior to pregnancy but there is currently little evidence to guide management in these situations.

EPILEPSY

All women with epilepsy are likely to have considered the impact their condition and its treatment might have on their ability to have and bring up children. For example, a postal survey of 12,000 female members of Epilepsy Action (a UK patient charity) obtained 2000 responses. The most important issues highlighted by women 19–44 years were risk of epilepsy/medication affecting the unborn child (87%), effect of pregnancy on seizure control (49%), and risk of child developing epilepsy (42%).

Anecdotally, these considerations are also affected by broader social and economic factors. For example, women may weigh the effects of pregnancy and family on their employment in a way that differs from women who do not have epilepsy. As has been described previously, women with epilepsy are over-represented in areas of socioeconomic deprivation, and this may affect choice of partner. Furthermore, women may be concerned about their partner and relationship – feeling they may need to rely more on them than other women.

The history of advice given to women with epilepsy about their ability to have children has reflected a great uncertainty and some prejudice against women with this condition. Anecdotally, older women with epilepsy report being told in no uncertain terms not to conceive by their doctors.

Over the past 40 years, women have not been so actively dissuaded from having children. Nevertheless, ideally, a woman should be informed of the full matrix of consequences arising from the interactions of (1) the epilepsy syndrome; (2) seizures; (3) co-morbidities or other relevant health issues, such as smoking or alcohol consumption; and (4) anti-epileptic drugs (AEDs), and these should be discussed with respect to the obstetric and fetal outcome of pregnancy[43].

Fertility

Overall, fertility rates among women with epilepsy are slightly lower than the general population. A number of epilepsy and non-epilepsy related explanations for this observation have been offered.

1. Women with epilepsy may find it difficult to establish or maintain relationships with men and therefore not be in a position to consider planned pregnancy. A number of studies demonstrate that such women are less likely to marry or remain in relationships than women without epilepsy[44].
2. Seizures may have an adverse effect on the menstrual cycle. In one study, over 35% of women with partial seizures of temporal origin had anovulatory cycles when studied over three cycles, compared to 8% of controls. The authors considered that seizures might have a direct effect on the hypothalamic–pituitary axis, independent of drug effects.
3. Certain AEDs have been highlighted to have particular effects on the female reproductive system. Valproate (VPA) has been associated with polycystic ovary syndrome in a number of species, including humans[45], although the strength of this association has been contested (see below).
4. Fertility may be reduced because of non-epilepsy related factors. Women may be overweight, smoke or consume too much alcohol – all of which may reduce their ability to conceive.

Thus, female fertility may also be affected by the epileptic syndrome, severity of seizures and other co-morbidities independently of the effects AEDs[46–50].

Epilepsy is more prevalent among women of low socioeconomic status (SES), and this may also have an impact on observed fertility rates, although this aspect of care has not been directly investigated. Traditionally, fertility rates among low SES women are higher than among high SES, although pregnancy outcomes are better in the latter group.

Effect of pregnancy on epilepsy

Anecdotally, most women express concern about how becoming pregnant might affect seizure control. Even women who are seizure-free while taking an AED are concerned about the medical implications (injuries, mortality, psychiatric effects) or the social consequences (for example loss of driving licence) of a breakthrough seizure.

The risk that seizure control may deteriorate has been considered in a number of studies, recently summarized in a comprehensive literature review[51]. In this review, the percentage of patients with unchanged seizure frequency in these studies ranged from 54 to 80%. The highest rate of unchanged seizure frequency was the 80% reported in AED-compliant patients, documented by serum levels. The rate of seizure decrease ranged from 3 to 24%. The rate of seizure increase ranged from 14 to 32%. Unfortunately, interpretation of these

studies is limited as none included a 'control' group of women with epilepsy who were not pregnant: epilepsy is well known to 'ebb and flow' with seizure frequency spontaneously changing over periods of months or years.

There are several reasons why women with epilepsy may suffer increased risks of seizures during pregnancy. Specifically, AEDs which have previously controlled epilepsy, may become less effective for a number of reasons:

1. Women may take their treatment less regularly or stop altogether because of first trimester nausea, or fear of the potential risks from AEDs to the fetus[52]. As is always the case with non-adherence, this may not be reported at the time to the physician.
2. Particularly in the later stages of pregnancy, women may be more sleep deprived, which can trigger seizures in susceptible individuals even when AEDs are taken.
3. Drug metabolism and drug effects are different in pregnancy. The state of pregnancy induces significant changes in protein binding of hormones and exogenous compounds such as AEDs – leading to a fall in 'free' drug concentrations – particularly in the final trimester. Additional pharmacokinetic changes in drug clearance may result in reduction in available drug. Certain AEDs, such as lamotrigine (LTG) are particularly prone to this effect[53].

Delivery is a time of particular concern. Seizures occurring around the time of delivery can result in both maternal and fetal harm[54] compounding the hemodynamic and physical stresses associated with labor. It is commonly quoted that for 2–4% of women with epilepsy, delivery will be associated with seizures during labor or in the following 24 hours, although the evidence for this statement is approximately 20 years old[55] and may reflect previous obstetric practice with respect to women with epilepsy.

Effect of seizures occurring during pregnancy

Women with epilepsy are familiar with the effect that seizures may have on their own person. They are typically aware but less certain about the effects seizures may have on the developing fetus.

There has been a longstanding awareness that tonic–clonic seizures may cause abnormalities in fetal heart rate[56,57]. Higher miscarriage rates have been observed, but have also been associated with there being family history of epilepsy, particularly either parent having epilepsy[58]. The published data include case reports where pregnant women have suffered seizures while the fetal heart rate has been monitored, and fetal distress was documented[54]. Nevertheless, population studies to inform clinicians and patients about the relationship between seizures and adverse fetal outcomes are less clear.

It is the generally held view that the occurrence of generalized tonic–clonic seizures during pregnancy may harm the fetus; although the absolute risk is low, it is likely to depend on the frequency and severity of seizures. There is insufficient evidence to quantify this risk. Partial seizures (simple or complex), absence seizures, or myoclonus are not harmful to the fetus[43].

Nevertheless, a more recently published prospective study of cognitive function in children exposed to AEDs *in utero* reported that the type of seizure (focal or generalized) or occurrence of more than five convulsive seizures during pregnancy was not significant within a regression model[59]. This finding contrasts with previous data[60] and its significance is further limited because in common with all previous work the study was not statistically 'powered' to consider this association, indeed the proportion of patients with poorly controlled epilepsy was small: only eight pregnancies of 303 mothers were exposed to more than eight convulsive seizures.

The effects that might be induced by prolonged seizures are also not well documented. For example, early reports suggested prolonged seizures in the form of status epilepticus may result in significant fetal (and maternal) mortality rates. Status epilepticus is defined as a seizure persisting for more than 30 minutes. An early report by Teramo *et al*.[54] documented 29 cases from the literature of which nine of the mothers and 14 fetuses died.

More recently, the EURAP study[61] reported that seizure frequency presented a low risk of adverse pregnancy outcomes such as spontaneous abortions, stillbirth and perinatal deaths. Of 36 cases of status epilepticus (12 convulsive) there was one stillbirth but no cases of miscarriage or maternal mortality. Although they reflect the findings of a large and respected pregnancy registry, these findings provide only limited guidance to neurologists and women with epilepsy: status epilepticus is usually associated with significant metabolic and hemodynamic compromise, and risk of death is high. For example, a large North American epidemiological study demonstrated overall mortality rates associated with status epilepticus were 22%[62] – similar to results obtained from other studies over many years. In contrast the EURAP study recorded a mortality rate of 0%, which suggests that the episodes of status epilepticus recorded in the EURAP study differed significantly from those considered in previous studies. It must be assumed that the cases of status epilepticus in EURAP were somehow milder, or differed in definition from other studies.

Overall, one of the key issues that doctors and women with epilepsy struggle with is the need to balance control of seizure frequency and severity with the potential adverse effects of AEDs during pregnancy. In particular, women on high doses of AEDs, on non-first line AEDs and/or polytherapy are generally those with the most severe or enduring epilepsy. VPA presents a particular challenge for clinicians and women with epilepsy. VPA is a first-choice treatment for many idiopathic generalized epilepsies, which may relapse if treatment is changed or stopped. The failure of the reported studies to account adequately for the effect of seizure frequency and severity on pregnancy outcome makes counseling individual patients particularly difficult.

In general, however, the main aim for women with epilepsy in pregnancy is to remain seizure free, and they are therefore advised to continue AEDs during pregnancy to avoid seizures. Exceptions occur if the risk of seizures is very low, the seizures can be avoided in some other way or the seizures are mild (i.e. non-convulsive seizures)[43]. This decision making is summarized below.

Significance of epilepsy type in pregnancy

Some epilepsies are associated with underlying conditions that have a strong genetic predisposition. In these cases, women will need to be given genetic counseling about the likelihood that their children may suffer epilepsy, or the condition that may underlie the woman's epileptic condition.

For example, women whose epilepsy is caused by Mendelian genetic conditions, such as subependymal heterotopia, neurofibromatosis or tuberous sclerosis will need to be aware that these disorders may have up to a 50% chance of being expressed in any child.

Women with learning disabilities for whom the underlying diagnosis is not clear – and whose neurological problems are likely to be due to a combination of the effects of several genes and environment – are more difficult to counsel. Nevertheless, maternal IQ and home social environment are the strongest predictors of a child's IQ[63]: maternal learning difficulties are likely to adversely affect child neurodevelopment in both respects.

Women with idiopathic generalized epilepsies, particularly absence epilepsies and juvenile myoclonic epilepsy are told that the

likelihood of their children developing a similar disorder is in the order of 5–20%. It is not normal practice to counsel women about the subtle cognitive abnormalities that have been noted in some neuropsychometric studies of women with these conditions – as too little is known about the magnitude of these effects.

Effect of co-morbidities and other health-related issues on pregnancy outcome

Women with epilepsy who are pregnant or who are planning pregnancy may present with non-epilepsy related factors that may affect pregnancy outcome.

Many of the co-morbidities frequently seen in people with epilepsy (such as mental health disorders, learning difficulties and osteopenia) and their treatments may be relevant in terms of predicting or counseling about pregnancy outcome. For example, some antidepressants or antipsychotics may have established teratogenic potential.

Women may also present with specific obstetric risk factors (such as history of premature labor, spina bifida or occurrence of other birth defects), which may modify advice given in relation to epilepsy and AEDs.

Low SES is a further risk factor that is known to be associated with poor pregnancy outcomes. As has been described, women with epilepsy frequently come from low SES households (i.e. partners may be of low SES) or neighborhoods. Low SES is known to be associated with adverse obstetric and fetal outcomes including low birth weight, perinatal, neonatal and postnatal mortality, and also of non-chromosomal congenital malformations[64–66].

Furthermore, low SES and poor early household environment are also associated with poor early neurodevelopment. This issue is relevant when considering the teratogenic effects of drugs used during pregnancy. For example, children exposed to cocaine *in utero* were assessed and consideration given to whether they had been placed in foster care or remained with parents. Children placed in foster care were likely to have been exposed to higher doses of cocaine. But postnatal neurodevelopment among the fostered group was superior (although not equivalent to 'normal') highlighting the importance of the early environment.

Certain behaviors such as alcohol consumption and smoking are well known to be detrimental to pregnancy outcome[67]. Folic acid should be taken[68], although whether it protects the fetus from neural tube defects in epilepsy is less clear.

The above non-epilepsy related factors can have a significant effect on the outcome of a pregnancy. It is important that those interpreting the research data and guidelines, and counseling women with epilepsy about pregnancy are aware that non-epilepsy related factors may modify risks presented to women in this context. The extent to which this is the case in neurology (and obstetric) practice in the UK is not certain.

Effect of anti-epileptic drugs on pregnancy outcome

Without epilepsy, and without AEDs, on average women face an overall risk of approximately 2% of bearing a child with a major congenital malformation (MCM). Furthermore, it is estimated that 3.6% of children at school age will be identified as having a primary special educational need associated with learning difficulties. A higher proportion, in the region of 20%, will require some form of learning support at school.

The possibility that AEDs may adversely affect the development of the fetus to increase the risk of congenital malformations has been recognized for many years in a range of studies, published since before the 1970s[69]. In particular, a number of pregnancy registries in North America, Europe, UK and Australia have

been set up to monitor pregnancy outcomes in women taking AEDs[70–73] and one company register was set up to monitor LTG only[74]. These registries are described in the report of Morrow[71]. These registries share in common the fact that only first trimester exposures are considered, and that the greatest focus is on the presence of MCMs. Meta-analysis of their findings suggests that the risk of MCM is increased approximately three-fold[75]. In particular women taking two or more drugs ('polytherapy') have more than a 10% chance of having a child with a congenital malformation.

It has been this range of studies, combined with the warnings about potential teratogenicity from the manufacturer, and latterly data from the registry studies that has led clinicians to warn patients about potential teratogenic effects and, where possible, to restrict the dose of AED treatment to a single agent, and, if possible, to review dose or consider withdrawal. This strategy depends significantly on the patient's condition. For example, many of the idiopathic epilepsies – and particularly juvenile myoclonic epilepsy – are likely to relapse if the dose is reduced too much or treatment is stopped. Importantly, it is also these epilepsies that best respond to VPA.

Over the past 15 years, new AEDs have become available to treat different types of epilepsy. With greater choice of AEDs, there has been corresponding interest in the differential effects individual AEDs may have on fetal development, in terms of rates of both congenital malformations and neurodevelopment. It is hoped that women who may become pregnant can be commenced on, or switched to, AEDs with potentially less teratogenic effects.

Data have been derived from animal studies[76], from a range of case reports, retrospective observational studies and prospectively collected from women with epilepsy. Over many years, many AEDs have been implicated in causing additional MCM and neurodevelopmental delay – for example phenytoin[77,78], phenobarbital and carbamazepine (CBZ)[79]. But over the past 5 years, there has been increasing emphasis on the possible differential effect of VPA.

The pregnancy registries, together with other published series, also imply a differential effect of AEDs on fetal outcomes. This has intuitive appeal, as although AEDs all have in common a capacity to suppress or prevent seizures, they are often very different chemical entities. In all the registry studies, consistently higher rates of congenital malformations are seen with VPA compared with CBZ or LTG[70–73,80]. The data provided do not indicate any particular pattern of malformations, with the exception of neural tube defects being more strongly associated with VPA, an association which has long been suspected[81,82].

There are many difficulties with the interpretation of these data and their application to clinical practice. The most commonly cited problem is 'indication' bias and the possibility that outcomes measured by the epilepsy registries, or even prospective cohorts may be confounded by factors including co-morbidities, parental (including paternal) genetic and mental health, and socioeconomic status.

Three specific areas of concern about indication bias have been expressed. First, women treated with VPA differ in terms of the underlying epileptic condition. Until recently, VPA was first choice treatment for women with idiopathic generalized epilepsy, as it was perceived to be more effective, whereas partial onset epilepsies (with or without secondary generalization) were treated with CBZ (or latterly LTG). Idiopathic generalized epilepsies have a strong genetic propensity, and concerns have been expressed that any increased rate of MCM or neurodevelopmental delay may reflect the underlying condition rather than a specific teratogenic effect.

Second, there is clear evidence that use of VPA has fallen significantly since concerns have been raised about its teratogenicity. Publications and guidelines now routinely highlight VPA as having poorer fetal outcomes,

and practice has been observed to change[83]. These trends in prescribing have also been demonstrated by the pregnancy registries. For example, the Non-Epileptic Attack Disorder (NEAD) registry reported that whereas in 1999, 17% of subjects reported using VPA in the first trimester, by 2008 this proportion had fallen to just 3%. Although no study has investigated the types of patient now treated with VPA, it must strongly be suspected that those who have continued to be treated with VPA over the past 10 years must differ significantly from those who are not. It is likely they have more difficult to treat epilepsy (with co-morbidities) and do not tolerate or achieve seizure control on alternative drugs. Poorly educated women, with poor access to medical services – who might be expected to have poorer outcome in any case – might remain on VPA through omission to change the AED, although evidence to support this assertion is only anecdotal.

Third, the dose-dependent effect observed for VPA (and some other AEDs) may also in part be due to patients with more severe underlying conditions requiring a greater dose of VPA. Plasma concentrations are not helpful in this regard as serum levels of VPA vary by more than 100% through a 24-hour period and their measurement is of little clinical utility save for the purpose of identifying possible non-compliance with treatment regimens.

Significant confounders, such as co-morbidity, may be relevant.

Obstetric outcomes

Poorly controlled epilepsy is generally held to be associated with poor fetal and obstetric outcomes. For example, an authoritative review stated that women with epilepsy have been observed to have a greater incidence of complications such as eclampsia, preterm delivery, spontaneous abortion and induced labor[68]. In the UK between 2003 and 2005, women with neurological conditions accounted for 37 out of a total 87 maternal deaths, with epilepsy ($n = 11$)[1] accounting for a significant proportion of these deaths.

These statistics underpin general advice that the obstetric care of women with epilepsy should include close liaison between obstetrician and neurologist.

In common with many other epilepsy outcomes clinicians and patients struggle to extrapolate the observations in published research and of general guidelines to their own specific cases. Many women with epilepsy seek to avoid an over medicalized pregnancy, which they may perceive to be 'spoilt' by numerous medical appointments and investigations.

A recent authoritative consensus document[67,84] reviewed all evidence in this area. The conclusions were vague, and were unable to distinguish between women with mild epilepsy and those who suffered frequent generalized seizures: 'for WWE [women with epilepsy] who are taking antiepileptic drugs (AEDs), there is probably no substantially increased risk (>2 times expected) of cesarean delivery or late pregnancy bleeding, and probably no moderately increased risk (>1.5 times expected) of premature contractions or premature labor and delivery. There is possibly a substantially increased risk of premature contractions and premature labor and delivery during pregnancy for WWE who smoke...'

Thus in everyday practice, it is recommended that there is good liaison between obstetrician and epilepsy specialist, that care should be taken to optimize AED doses at different stages through the pregnancy, and that delivery should take place in an obstetric unit with facilities for maternal and neonatal resuscitation and treating maternal seizures[43]. The optimization of AED dose is case specific. Individuals vary in terms of their seizure threshold and metabolism of drugs. The consequence of a seizure for that individual must also be considered. For example, a woman with a history of status epilepticus, or who has been seizure free for more than 12 months and holds a driving licence, is usually extremely reluctant to reduce drug doses to a level that may compromise seizure threshold.

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12

Optimization of hypertension and embryo safe antihypertensives

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Hypertension is the commonest medical complication of pregnancy, affecting 5–10% of all pregnant women. It is a major cause of maternal mortality[1] and contributes significantly to perinatal morbidity and mortality. The specific risks are related to disease severity and the presence of hypertensive target organ involvement. Maternal and fetal outcomes are optimal if pre-existing hypertension is well controlled before pregnancy. This chapter provides an overview of the different hypertensive disorders of pregnancy and highlights the importance of preconception assessment and counseling to optimize pregnancy outcome. The advantages and disadvantages of different antihypertensive drugs in pregnancy are also summarized.

HYPERTENSIVE DISORDERS OF PREGNANCY

Pregnancy may be complicated by four types of hypertensive disorders: chronic (pre-existing) hypertension, gestational hypertension, pre-eclampsia–eclampsia and chronic hypertension with superimposed pre-eclampsia. These disorders differ in maternal and fetal prognosis and the type of pre-pregnancy assessment and counseling required.

Chronic hypertension

Chronic hypertension is present before pregnancy, diagnosed before 20 weeks' gestation, or persistent beyond 12 weeks' postpartum. It may be primary or secondary. Primary hypertension accounts for 90% of chronic hypertension in pregnancy. Simply put, this is essential hypertension with multifactorial predisposing factors, including genetics and ethnicity. Ten per cent of pregnant women with chronic hypertension have underlying secondary causes including endocrine disease (diabetes mellitus, pheochromocytoma), renal disease (glomerulonephritis, renovascular disease) or connective tissue disorders (systemic lupus erythematosus, scleroderma). Chronic hypertension is classified as mild (stage 1), moderate (stage 2) or severe (stage 3), depending on the level of blood pressure and the presence of target organ involvement. Mild hypertension is a systolic blood pressure (BP) of 140–149 mmHg or a diastolic BP of 90–99 mmHg. Moderate hypertension exists when systolic BP is 150–159 mmHg or diastolic BP is 100–109 mmHg, and severe disease is defined as systolic BP ≥160 mmHg or diastolic BP ≥110 mmHg. The disease is considered severe in the presence of target organ (such as kidney and cardiac) involvement regardless of the level of blood pressure. The diagnosis of chronic hypertension may be missed in early pregnancy because of the physiological fall in blood pressure during the first half of pregnancy; however, it should be considered if the first trimester diastolic blood pressure values are in the 80s. It may also be misdiagnosed as gestational hypertension if the patient

first presents in late pregnancy. The diagnosis should also be considered in women who develop recurrent hypertension in pregnancy.

The prevalence of chronic hypertension varies depending on the population studied. Unfortunately, it appears to be rising across all populations, partly due to the increasing body mass index (BMI) of the general population and also due to the current pattern of childbearing in women of advanced age. The health and financial burden of looking after pregnant women with hypertension will increase in the future as more resources are required to meet the cost of additional laboratory tests and more frequent antenatal monitoring.

Maternal complications result from severe hypertension or superimposed pre-eclampsia and include acute left ventricular failure, acute renal failure, intracranial hemorrhage (stroke) and placental abruption. Fetal complications such as preterm delivery, intrauterine growth restriction (IUGR) and increased risk of stillbirth are also related to severe hypertension, superimposed pre-eclampsia and placental abruption. For most women with mild to moderate chronic hypertension, the risks of maternal or perinatal morbidity and mortality are moderate compared to normal pregnancy. However, these are increased significantly in severe hypertension, when maternal age is greater than 40 years, chronic hypertension has been present for more than 5 years, or co-existing medical disorders (such as diabetes, renal disease connective tissue disease, cardiac disease) are also present[2,3].

Gestational hypertension

Gestational hypertension is new onset hypertension after 20 weeks' gestation in the absence of proteinuria. Hypertension is defined as systolic BP ≥140 mmHg and/or diastolic BP of ≥90 mmHg on at least two occasions, at least 4 hours apart and resolving within 12 weeks after delivery. The disease is considered severe if systolic BP is ≥160 mmHg and/or diastolic BP ≥110 mmHg[4]. Gestational hypertension is part of the pre-eclampsia–eclampsia spectrum of disorders and accounts for up to 25% of the syndrome. Up to 25% of cases may progress to pre-eclampsia, and although the rate of progression is unpredictable, it appears to be dependent on the gestational age at onset. For example, Barton *et al.* provided evidence that the risk of pre-eclampsia may increase to up to 50% if gestational hypertension occurs before 30 weeks' gestation[5]. Fortunately, most cases of gestational hypertension are mild to moderate, occur close to term and the risk of poor fetal outcome is only slightly greater than in normal pregnancy. However, severe or early onset disease is associated with significant adverse perinatal outcomes such as IUGR. Women with severe gestational hypertension should therefore be managed in a similar manner to those with severe pre-eclampsia[4].

Pre-eclampsia

Pre-eclampsia is a multisystem disorder of the second half of pregnancy diagnosed by new onset hypertension and proteinuria after 20 weeks' gestation with resolution of both within 12 weeks' postpartum. Hypertension is defined using an absolute cut-off systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg on at least two occasions and at least 4 hours apart. Proteinuria is defined as more than 300 mg urinary protein excretion in 24 hours. Underlying chronic renal disease should be suspected if proteinuria is present before 20 weeks' gestation or persists beyond 12 weeks after delivery. Proteinuria of pre-eclampsia results from glomerular endotheliosis and is part of the underlying generalized endothelial dysfunction. Eclampsia is the occurrence of seizures superimposed on pre-eclampsia. The diagnosis of pre-eclampsia should be strongly considered if gestational hypertension is associated with persistent symptoms, or the presence of thrombocytopenia or abnormal liver enzymes.

Pre-eclampsia is classified as severe if any of the following are present: (1) proteinuria ≥5 g in a 24 hour period; (2) evidence of multiorgan involvement such as oliguria or pulmonary edema; (3) platelet count <100,000 per mm; (4) abnormal liver enzymes associated with upper abdominal pain (epigastric or right upper quadrant); or (5) persistent signs or symptoms of cerebral irritation (headache, blurred vision, altered mental state)[6]. Unlike chronic hypertension, the hypertension of pre-eclampsia is a secondary manifestation of the disease and contributes to some of its consequences including intracranial hemorrhage or abruption. Severe pre-eclampsia is associated with increased maternal morbidity such as acute renal failure, liver hemorrhage or failure, disseminated intravascular coagulopathy and cerebral hemorrhage. Such complications are common in women with underlying medical conditions and when pre-eclampsia occurs before 32 weeks' gestation. Severe disease is also associated with a 2% increased risk of maternal mortality; the commonest cause of maternal death in pre-eclampsia in the developed world is intracranial hemorrhage[1]. Perinatal complications include increased risk of stillbirth, IUGR and preterm delivery. These risks are significantly greater in women who develop early onset pre-eclampsia but less common if the disease occurs after 36 weeks' gestation.

Pre-eclampsia superimposed on chronic hypertension

About 25% of pregnant women with chronic hypertension develop superimposed pre-eclampsia. This is defined as the onset of new signs or symptoms of pre-eclampsia after 20 weeks' gestation in a woman with chronic hypertension. Making the diagnosis may be difficult, and distinguishing superimposed pre-eclampsia from worsening chronic hypertension requires a high index of suspicion. The diagnosis should be considered if a woman with chronic hypertension develops significant new onset proteinuria after 20 weeks' gestation. Other criteria include: (1) a women with hypertension and proteinuria before 20 weeks' gestation who develops increased proteinuria during the second half of pregnancy; (2) a sudden increase in blood pressure in a woman whose hypertension has previously been well controlled; (3) platelet count <100,000 cells/mm^3); and (4) abnormal liver enzymes (ALT or AST). The risk of superimposed pre-eclampsia is greater if the chronic hypertension has been present for 5 years or longer, associated with impaired renal function or a history of superimposed pre-eclampsia exists from a previous pregnancy. Maternal and fetal prognosis is worse than in *de novo* pre-eclampsia. Once the diagnosis is made, clinical management is similar to severe pre-eclampsia.

PRECONCEPTION COUNSELING OF WOMEN WITH CHRONIC HYPERTENSION

The general aim of preconception counseling is to assess the overall health of the woman, identify any undetected health risks or disease(s), change medication(s) to safer alternatives in pregnancy, and to estimate baseline function(s) for future reference[7]. Ideally any woman planning a pregnancy should have preconception counseling 3–6 months before conception. Unfortunately this goal is poorly achieved, as most pregnancies are unplanned[9]. Counseling is particularly useful in women with pre-existing hypertension, to allow enough time to evaluate the severity of disease and to assess possible reversible secondary causes. In addition to review of antihypertensive medication(s), advice should be offered about lifestyle modifications prior to conception and how the hypertension will

affect future pregnancy. Lifestyle modifications include smoking cessation, reduced alcohol consumption, exercise and reduced salt intake, particularly in black women, as these are well established cardiovascular risk factors. Although data on the effects of salt restriction during pregnancy are inadequate, many agree that the recommended daily intake of 2.4 g still applies during pregnancy. Excessive alcohol intake may aggravate maternal hypertension, whereas smoking increases the risks of abruption and IUGR. Women with a high BMI should be encouraged to lose weight, as obesity is an independent risk factor of adverse pregnancy outcome. A program of exercises and appropriate dietary modifications should be recommended well before pregnancy to allow enough time for weight loss. Although regular exercise is beneficial for non-pregnant women with hypertension and safe during normal pregnancy, data on its safety in pregnant women with chronic hypertension are limited. Weight loss during pregnancy even in obese chronic hypertensives is not recommended, and there is no evidence this reduces the risk of superimposed pre-eclampsia.

The woman's medical records should be reviewed, physical examination performed and relevant tests carried out to evaluate hypertensive target organ complications such as left ventricular hypertrophy, retinopathy and renal disease. Physical examination should include assessment of the carotid, femoral and peripheral pulses, palpation of the kidneys for possible polycystic kidney disease and auscultation for renal artery bruits to exclude renovascular disease. Fundoscopy should be performed to elucidate evidence of arterial disease. Blood urea electrolytes and creatinine are essential to assess renal function. Urine analysis and culture should be performed, and 24 hour urine collection for protein and creatinine clearance requested if indicated. These tests also form a baseline for future reference. Women with underlying renal disease have a higher risk of adverse perinatal outcome independent of superimposed pre-eclampsia and the risk of fetal loss is increased significantly if the blood pressure is poorly controlled[8,9]. A chest X ray, electrocardiogram (ECG), echocardiogram (if long-standing hypertension) and blood test for antinuclear antibody to exclude possible lupus nephropathy should be considered in women with severe hypertension. Thrombophilia screen should be considered if there is a history of venous thromboembolism or recurrent pregnancy loss. Younger women with chronic hypertension usually require more detailed investigation as they are more likely to have a secondary cause. Twenty-four-hour urinary catecholamine metabolites should be assessed to exclude pheochromocytoma if there is a history of sweating or palpitation associated with paroxysmal or severe hypertension. Where indicated, renal imaging and angiography should be performed to exclude possible renovascular disease or adrenal gland pathology.

PRECONCEPTION COUNSELING OF WOMEN WITH PREVIOUS PRE-ECLAMPSIA

Women with a prior history of pre-eclampsia are at increased risk of recurrence during future pregnancies. The magnitude of this risk depends on the severity and gestational age at onset of the previous disease. Optimizing maternal health, including maintaining a normal BMI before pregnancy, is likely to reduce the risk of recurrence. During preconception counseling, a management plan should be formulated, which includes early antenatal booking, frequent monitoring of maternal and fetal well-being and timely delivery. If postnatal review and counseling were not carried out after the previous pre-eclamptic pregnancy, then tests should be performed to confirm reversal of target organ changes and to establish a baseline for future assessment.

PREDICTION OF PRE-ECLAMPSIA

Women attending preconception counseling want to know their risk of developing pre-eclampsia. Unfortunately, our current lack of comprehensive understanding of the pathophysiology of this disease does not allow accurate prediction of future risk. Discussion should take into consideration the presence of chronic hypertension or other maternal risk factors including interpregnancy interval greater than 10 years, maternal age less than 18 years or greater than 35 years, and personal or family history of pre-eclampsia or underlying medical disorders[10,11]. Fetal factors likely to contribute to the risk of disease include multiple pregnancies and triploidy[12]. Currently, Doppler ultrasound of the uterine arteries remains the best tool available test for predicting pre-eclampsia. Persistence of uterine artery notching after 23 weeks appears to reflect failure of trophoblastic invasion. However, the predictive value of this test is only 30%, with a sensitivity and specificity of 75% and 96%, respectively[13].

PREVENTION OF PRE-ECLAMPSIA

Several interventions including low-dose aspirin and dietary supplementation such as calcium, magnesium, antioxidant vitamins and omega-3 unsaturated fatty acids (fish oil) have been investigated for prevention of pre-eclampsia; however, none has shown consistent benefit. Low-dose aspirin has long been considered for prevention of pre-eclampsia. Although several small trials initially suggested substantial benefit, these were not confirmed by larger, well designed, randomized controlled trials[14,15]. It is possible that aspirin studies in high-risk women showed variable outcomes because chronic hypertension was not distinguished from other high-risk conditions. Given that pregnancy outcomes in chronic hypertension are different from other conditions which may be mediated by different factors, the combination of high-risk women into a heterogeneous group may explain the failure of these studies to observe large benefits from aspirin supplementation. A recent Cochrane database meta-analysis established a 10% reduction in the relative risk of pre-eclampsia and preterm birth before 34 weeks and a 9% reduction of stillbirth[16]. In spite of the inconclusive data, low-dose aspirin may be considered on an individualized basis[17]. The optimum time to commence aspirin supplementation is uncertain, however. Most trials on aspirin were started after the first trimester, and although data on its effect on organogenesis are inadequate, its use in women with recurrent early pregnancy loss has not shown any adverse effect. A Cochrane meta-analysis database did not show any evidence of adverse effects when started earlier[18].

Dietary supplementation in pregnancy has not been shown to be effective in preventing pre-eclampsia in low-risk women. Although trials in high-risk nulliparous women have suggested that calcium decreased the risk of pre-eclampsia[19,20], no conclusive evidence shows that an enriched calcium diet beyond the daily requirement provides any benefit in pre-eclampsia prevention. Several studies have also investigated the potential benefit of magnesium supplementation in prevention of pre-eclampsia; however, none has shown any benefit[21,22]. Earlier studies suggested antioxidant vitamin supplementation reduced the risk of pre-eclampsia[23]. However, more recent randomized controlled trials have shown antioxidant therapy (vitamin C and E) does not prevent pre-eclampsia and may even be harmful[24,25]. Women in the preconception period should be encouraged to use the standard daily dietary requirement as part of a balanced diet and to maintain the daily elemental calcium dietary requirement of 1000 mg for general well-being.

ANTIHYPERTENSIVES IN PREGNANCY

Administration of any drug(s) in pregnancy presents a unique set of problems. Not only must the pharmacological mechanisms be considered when prescribing the agent, but the fetus must be kept in mind, as it also is a potential recipient of the drug. With rare exceptions, most substances cross the placenta and, depending upon their lipid solubility and structure, achieve varying concentrations in the fetus. In humans, the mechanisms by which drugs exert teratogenic effects are poorly understood. They may act on maternal receptors with indirect effect(s) on the fetus or may have direct effect(s) on the developing embryo and result in structural anomalies. They may affect the nutrition of the fetus by interfering with the passage of nutrients across the placenta. Many of the antihypertensive agents used in pregnancy appear to affect the fetus by this latter mechanism. The type and frequency of anomalies caused by a teratogenic agent depends critically upon the developmental stage of the fetus at the time of exposure[26]. Teratogenic effects of drugs are also dose and time dependent, with the greatest risk during the first 3 months of pregnancy. However, this may occur at any stage of pregnancy compared to postnatal exposure because of the high rate of cellular proliferation and differentiation in the fetus.

Some antihypertensive drugs are associated with unacceptable fetal and neonatal adverse effects and are therefore contraindicated in pregnancy. Women with chronic hypertension who are planning a pregnancy should be treated with medication that can be continued into pregnancy. Where this is not possible, because of co-existing medical disorders as in diabetic nephropathy, drugs that are not normally recommended in pregnancy such as angiotensin converting enzyme inhibitors could be considered. However, this should be changed to a suitable alternative as soon as pregnancy is confirmed. Antihypertensive therapy for severe hypertension is necessary to prevent maternal cardiovascular complications including intracerebral bleeding and left ventricular failure, about which there is no controversy concerning benefits. In contrast, the evidence base regarding drug treatment of moderate hypertension during pregnancy is too small to prove or disprove benefit. The argument in favor of drug treatment of mild to moderate hypertension is that it prevents severe hypertension and its associated complications.

The adverse effects of antihypertensive drugs may be different in chronic hypertension and in pre-eclampsia because of differences in underlying pathophysiology, such as the placental pathology of pre-eclampsia. The timing, dosage and duration of antihypertensive drug treatment may also contribute to adverse effects. For example, women with moderate chronic hypertension are more likely to require medication for a longer duration compared to those with pre-eclampsia. The true incidence of adverse effects of antihypertensive drugs in pregnancy is difficult to quantify, as data on adverse effects are limited and are usually based on surveillance studies and case reports. Assessing causality from surveillance studies and case reports may not be accurate because of lack of previous exposure data, inability to separate specific effects in multidrug regimens and difficulty in calculating rates of adverse events.

GOALS FOR TREATING HYPERTENSION IN PREGNANCY

No agreement exists regarding the threshold blood pressure beyond which antihypertensive treatment should be started in mild to moderate hypertension in pregnancy. Threshold values between 160/100 mmHg and 140/90 mmHg have been suggested in the absence of target organ damage. Consensus exists, however, that a lower blood pressure

for starting treatment should be considered in the presence of target organ dysfunction. Aggressive control of hypertension is likely to increase the risk of IUGR, because very low maternal blood pressure is associated with low birth weight and increased perinatal mortality[27]. It may be necessary to reduce the dosage or even temporarily discontinue antihypertensives during the first half of pregnancy because of the physiological decline in maternal blood pressure. On the other hand, higher dosage may be required in chronic hypertension during the second half of pregnancy to prevent severe hypertension, although this strategy may not prevent the development of superimposed pre-eclampsia.

ANTIHYPERTENSIVE DRUGS

Antihypertensive drugs are classified, depending on their mechanism of action, into centrally acting drugs, adrenoreceptor antagonists, direct vasodilators, angiotensin converting enzyme inhibitors and receptor blockers, and diuretics. Because of their common mechanisms of action, drugs within each category tend to produce a similar spectrum of adverse effects.

Centrally acting drugs

This group of antihypertensives inhibits sympathetic outflow from vasopressor centers in the brain stem and is associated with unpleasant maternal adverse effects. The commonly used centrally acting drugs in pregnancy are methyldopa and clonidine.

Methyldopa

Worldwide, methyldopa is the most widely used antihypertensive drug in pregnancy, mainly because of its apparent safety, and partly because it is less expensive than some others[28]. It is, however, not useful for acute control of severe hypertension in pregnancy because of its delayed onset of action. It is also the best studied antihypertensive drug in pregnancy in terms of risks to the fetus. In this regard, it does not appear to exert adverse fetal effects[29]. Although data on first trimester use are limited, no evidence of a significant increase in congenital anomalies is present. It also has the longest neonatal and infant follow-up studies (up to 7.5 years). Its unpleasant maternal side-effects including sedation, tiredness, depression and sleep disturbances, make it unsuitable for managing postnatal hypertension. Adverse effects observed in non-pregnant women, such as lichenoid drug erruptions, agranulocytosis, autoimmune thrombocytopenia drug-induced hepatitis, pancreatitis and parkinsonism, are very rare in pregnancy, possibly because of the short duration of use in pregnancy.

Clonidine

Clonidine is not the drug of choice for hypertensive therapy in Europe and North America. In the absence of controlled trials on its use in moderate chronic hypertension, surveillance studies have not shown significant increases in major birth defects. An excess of hyperactivity and sleep disturbance has been reported in 22 children with mean age 6 years, who were exposed to clonidine prenatally[30].

Adrenoreceptor antagonists

The antihypertensive effect of this class of drugs is mediated primarily by reducing cardiac output. Adrenoreceptor blockers are divided into alpha adrenergic blocking agents (alpha blockers) and beta adrenergic blocking agents (beta blockers).

Alpha blockers

Alpha blockers, such as prazosin, act by preventing the release of noradrenaline from postganglionic adrenergic neurons. Prazosin causes a rapid fall in maternal blood pressure, and fetal blood levels are 10–20% of maternal levels. It is, therefore, not suitable for use in pregnancy. Furthermore, fetal transverse limb defects have been reported following its use[31]. This group of adrenoreceptor antagonists is thus not recommended in pregnancy because of fetal adverse effects.

Beta blockers

Beta blockers are the second most commonly used antihypertensives in pregnancy after methyldopa and are widely prescribed in Europe and Australia. Their main mechanism of action is reduction of cardiac output by decreasing heart rate and myocardial contractility. Selective beta blockers, such as atenolol, are widely used in the non-pregnant state, because they have fewer side-effects due to cardioselectivity and also because they are administered once daily. They appear to be equally safe and effective as methyldopa. Whereas cardiac output is increased in the non-pregnant chronic hypertensives, it is reduced in pregnancies complicated by IUGR or pre-eclampsia. However, a large retrospective study of atenolol use in pregnancy suggested it may be associated with IUGR, especially when administered in early pregnancy and continued for a longer duration[32]. Evidence suggests that atenolol impairs fetomaternal circulation and increases uterine artery resistance index (RI) and fetal aortic pulsatility index (PI)[33]. Evidence also suggests that beta blockers may have long-term adverse effects on very low birth weight neonates, resulting in increased neonatal mortality. In this study, seven out of 19 infants (27%) exposed to beta blockers *in utero* died within 15 days after birth compared with those born to mothers on other antihypertensives[34]. Atenolol is thus best avoided in pregnancy, particularly if it is complicated by pre-eclampsia or IUGR because of reduced maternal cardiac output and uteroplacental perfusion.

Non-selective blockers, such as oxprenolol, have intrinsic sympathomimetic activity and lower blood pressure mainly by decreasing vascular resistance and depressing cardiac output to a lesser extent compared to other beta blockers. Their use in pre-eclampsia is therefore less likely to be harmful than that of selective beta blockers. However, non-selective beta blockers may precipitate asthma, and should be avoided in such patients. These agents also impair glucose tolerance and interfere with metabolic and autonomic responses to hypoglycemia and should be avoided in diabetics. Isolated cases of neonatal hypoglycemia[35] and bradycardia[36] have been reported; there were no long-term consequences, however.

Combined alpha and beta blockers

Combined alpha and beta blockers, such as labetalol, lower blood pressure by peripheral vasodilatation without compromising the maternal cardiovascular system. Labetalol is the commonest adrenoceptor antagonist and the second most studied antihypertensive used during pregnancy after methyldopa. It is well tolerated and does not appear to be teratogenic, although data on this point are limited in human pregnancy[37]. It has only 25% of the beta blocking effects and achieves blood pressure control while maintaining renal and uterine blood flow. One study suggested its use in established pre-eclampsia may reduce the amount of proteinuria[38]. There is, however, evidence that it may increase the risk of IUGR in spite of its vasodilatory effects, especially if started in second trimester[39]. Acute administration of labetalol causes a reduction in heart rate, peripheral resistance and blood pressure without abrupt maternal hypotensive effect and without interfering with uteroplacental circulation. Babies born after acute administration of labetolol for severe hypertension are less likely to have umbilical cord blood pH of less than 7.20 compared to those who have had hydralazine[39].

Vasodilators

Vasodilatory drugs, such as hydralazine, calcium channel blockers, diazoxide and sodium nitroprusside, act directly on blood vessel walls and reduce peripheral vascular resistance by different mechanisms. Diazoxide opens ATP sensitive potassium channels; calcium channel blockers prevent intracellular calcium flux, while sodium nitroprusside acts as a nitric acid donor. Diazoxide and sodium nitroprusside are not recommended for use in pregnancy because they are associated with acute fetal distress, intrauterine death and other undesirable fetal adverse effects[40].

Calcium channel blockers

These are vasodilators which act primarily by inhibiting extracellular calcium influx into smooth muscle cells through slow calcium channels, thus interfering with excitation–contraction coupling. Their vasodilatory effect is proportional to the degree of peripheral vasoconstriction, and therefore the extent of blood pressure reduction appears to be proportional to the pre-treatment blood pressure. Dihydropyridines such as nifedipine act predominantly on the peripheral vasculature, are antagonistic to all forms of vasoconstriction, and also exhibit a mild tocolytic effect. They are therefore useful in acute and long-term control of hypertension. Nifedipine is the commonest calcium channel blocker used in pregnancy. It is safe in therapeutic doses[41]; no teratogenic effects have been reported[42]; and it does not appear to adversely affect fetomaternal circulation when used for short- and long-term control of hypertension. However, severe maternal hypotension has been reported following administration of short-acting nifedipine for acute control of severe hypertension when administered sublingually or coadministered with magnesium sulfate[43,44]. Sublingual administration of nifedipine should be avoided to prevent rapid fall in maternal blood pressure. Nicardipine and nimodipine are also calcium channel blockers used in pregnancy; however, data on their safety and effectiveness are limited.

Hydralazine

Hydralazine decreases blood pressure by reducing peripheral vascular resistance. It causes direct vascular wall dilatation by as yet unexplained mechanism(s); however, it requires an intact endothelium to produce these effects[45]. It is more effective in lowering diastolic than systolic pressure. Its onset of action is 20–30 minutes even with parenteral administration. Hydralazine is the most commonly used drug for acute control of hypertension in pregnancy in North America. It is no more effective than intravenous labetolol; however, it is frequently associated with profound maternal hypotension and fetal distress from decreased fetoplacental perfusion. It is therefore more likely to result in urgent delivery by cesarean section with lower neonatal Apgar scores, compared to parenteral labetalol or oral nifidepine[46]. Abrupt and profound maternal hypotension resulting from hydralazine can be prevented by concomitant administration of a bolus of intravenous fluid. Although it is commonly administered intravenously for acute control of hypertension, it has also been used as second line therapy for long-term management of chronic hypertension. However, chronic administration may result in reduced renal perfusion pressure and fluid retention, thus

blunting its hypotensive effect. Data regarding its use during the first trimester and possible teratogenic effects are inadequate[37]. Hydralazine increases maternal heart rate and cardiac output from reflex sympathetic activation. This causes sustained release of noradrenaline resulting in tachycardia, flushing, nasal congestion, anxiety, restlessness and tremors. Headache is also a common side-effect due to dilatation of the cerebral venous circulation. Reported maternal adverse effects following chronic administration include hydralazine-induced lupus-like syndrome and hepatitis.

Diuretics

Diuretics deplete body water and sodium stores, and lower blood pressure by reducing blood volume and cardiac output. Their use in pregnancy remains controversial because of the potential to reduce or prevent physiological plasma volume expansion and therefore reduce uteroplacental perfusion. There is limited evidence that diuretics prevent plasma volume expansion[47], and women with chronic hypertension on diuretics do not increase their plasma volume to the same extent as occurs in normal pregnancy[47]. Since reduced maternal plasma volume is associated with impaired uteroplacental perfusion and fetal growth, diuretics should be avoided in pregnancies complicated by pre-eclampsia or IUGR. Their use in pregnancy is rare; however, teratogenic effects have not been reported. Maternal adverse effects including pancreatitis, hyperuricemia and hyperglycemia have been reported. Isolated adverse fetal and neonatal effects include fetal bradycardia, neonatal thrombocytopenia and neuroblastoma following *in utero* exposure. It a reasonable option to consider as a preconception antihypertensive in mild to moderate chronic hypertension. It may also be considered for postpartum management of hypertension. Frusemide is particularly useful for managing pulmonary edema complicating pre-eclampsia.

Agents that block production or action of angiotensin

This group consists of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). ACE inhibitors such as captopril, enalapril and lisinopril inhibit ACE. They reduce angiotensin and aldosterone production and thus decrease peripheral vascular resistance. They are widely used to treat hypertension in the non-pregnant state particularly if complicated by renal insufficiency or diabetes. The commonest maternal side-effect is dry coughing, and this is often the commonest reason for patient non-compliance. Angiotensin-II receptor blockers (ARBs) such as candesartan and losartan do not inhibit the breakdown of bradykinin, and thus are less likely to cause persistent dry cough.

ACE inhibitors are contraindicated in pregnancy, because they are associated with increased risk of fetal anomalies. Their use is associated with fetal renal failure, IUGR, oligohydramnios, pulmonary hypoplasia and fetal death[48]. Such fetal adverse effects appear to occur regardless of the gestational age at which these agents are administered. For this reason, care should be exercised when prescribing ACE inhibitors for women of childbearing age as a significant proportion of pregnancies are unplanned. It should be avoided in women with chronic hypertension who are planning a pregnancy, unless there is a compelling long-term indication such a history of diabetic nephropathy. In such cases the patient should be advised to inform her doctor as soon as she misses a period so that the ACE inhibitor can be changed to a suitable alternative. Data on ARBs use in pregnancy are limited. They should be avoided, as their mechanisms of action are similar to ACE inhibitors and they appear to have similar fetal adverse effects[49,50].

POSTNATAL HYPERTENSION AND ANTIHYPERTENSIVE THERAPY

The prevalence of postpartum hypertension is unclear and may represent a continuation of antenatal hypertension (recurrent) or appearance of a new hypertensive disorder (*de novo*). Women who develop postpartum hypertension are likely to stay in hospital longer after delivery, and this often results in anxiety about their recovery. Furthermore, severe hypertension may result in maternal mortality and vascular complications such as stroke. In spite of these risks, few data indicate the best method for managing women who develop hypertension after delivery.

General consensus exists that severe postpartum hypertension (systolic BP ≥160 mmHg or diastolic ≥110 mmHg) should be treated to prevent maternal vascular complications. However, there is no agreement on the benefits of treating mild to moderate disease, particularly when to start drug treatment and which treatment threshold to aim for. In spite of regular use of antihypertensive drugs for postnatal hypertension, little evidence exists for their safety and effectiveness. Data on safety of antihypertensives during breastfeeding are based on surveillance studies and case reports. A review of the available reports showed that the commonly used antihypertensives during pregnancy and breastfeeding such as methyldopa, beta blockers, combined alpha and beta blocker (labetalol) and nifedipine have minimal breast milk to maternal plasma ratios and are therefore safe during breastfeeding[50]. A recent Cochrane review has also shown no evidence that any of these antihypertensives are more effective than the other. The choice of antihypertensive drugs for postnatal hypertension should therefore be based on familiarity[51].

CONCLUSION

Hypertensive disorders of pregnancy are associated with increased adverse outcomes. Preconception counseling offers an opportunity to assess disease severity and ensure control before pregnancy, review antihypertensive agents already prescribed and change to safer alternatives, and formulate a detailed plan of management during pregnancy. It also provides an opportunity to counsel women with a previous history of pre-eclampsia and to discuss their risk of recurrence when this was not provided following the previous pre-eclamptic pregnancy. Although general consensus supports treating severe hypertension in pregnancy, the benefits and risks of antihypertensive drug therapy in a patient with a mild to moderate rise in blood pressure are still uncertain. All antihypertensive agents appear to cross the placenta and reach the fetus to different degrees, but there are inadequate data on the safety of antihypertensive drugs during pregnancy and evidence is limited to surveillance studies. There is no evidence that the commonly used antihypertensive drugs such as methyldopa, beta blockers, the combined alpha and beta blocker (labetolol) and calcium channel blockers (nifedipine) are associated with increased fetal or neonatal adverse effects. There is, however, convincing evidence that ACE inhibitors and ARBs are associated with significantly increased fetal adverse effects and should be avoided in pregnancy. The administration of antihypertensives to pregnant women with either pre-existing hypertension or pregnancy induced hypertension should be carefully discussed with the women by an experienced clinician.

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13

Women with severe mental illness

Ian Jones

INTRODUCTION: WHY IS MENTAL ILLNESS IMPORTANT?

The link between childbirth and severe mental illness has been described for hundreds if not thousands of years[1], but postpartum episodes are not merely of historical interest. Mental disorders in the perinatal period are of great public health importance in the 21st century – as illustrated by a number of cases in which women suffering from severe illness have killed themselves or harmed their infants[2], and by the findings of the Confidential Enquiries in the UK which find suicide to be a leading cause of maternal death[3–6]. Despite its undoubted clinical importance, perinatal mental illness has not received the attention, both in terms of clinical practice and research, that it clearly deserves.

The decision to start a family is fraught with difficulties for women with a history of severe mental illness as well as their partners. Such couples face a number of important questions and often encounter difficulties accessing the information they need. This chapter reviews what is known about severe mental illness in relation to pregnancy and childbirth. A number of issues are discussed, including the risk of childbirth impacting their illness, difficult decisions regarding medication in pregnancy, and questions that women and their partners may have about the risk of passing the illness on to their children.

WHAT EPISODES OF PSYCHIATRIC ILLNESS OCCUR RELATED TO PREGNANCY AND CHILDBIRTH?

Despite the widespread focus on postpartum depression, a wide variety of psychiatric disorders occur in relation to parturition – both in pregnancy and following childbirth. These include anxiety disorders, chronic psychoses such as schizophrenia, eating disorders and substance misuse. Pregnancy impacts on each of these conditions, and each, in turn, can have a significant effect on antenatal and postnatal care. Episodes may be the first presentation of a disorder or represent a recurrence of a pre-existing condition. Although many potential conditions may occur, attention is often focused on mood disorders and the trio of baby blues, postpartum depression and postpartum psychosis (Table 1).

The blues – over 50% of women experience a brief episode of minor mood change in the first postpartum week[8]. Such episodes are self-limiting, last no more than a few days, do not require treatment and should not be considered a 'disorder'.

Postpartum depression – significant depressive symptoms occur following more than 10% of deliveries and may last for months or even years[9]. Episodes of major depression at this time may cause significant emotional impairment and lead to severe long-term consequences. The symptoms of postpartum depression are no different to those of depression occurring at other times[10].

Table 1 The clinical features of postpartum psychosis, postnatal depression and the baby blues

	'Baby blues'	*Postnatal depression*	*Postpartum psychosis*
Incidence per delivery	~50%	~5–15%	~0.1%
Typical onset after delivery	Around days 2–5	Within 6 months	First 2 weeks
Duration	Few days	Weeks to months	Weeks to months
Symptoms	Depressed mood, irritability, lability of mood, crying	Depressed mood, lack of pleasure, poor sleep, poor appetite, suicidal thoughts, self blame, guilt	Elated, irritable or depressed mood, lability of mood, confusion/perplexity, psychotic symptoms including delusions and hallucinations, rapidly changing clinical picture
Treatment	Requires no intervention	Self help strategies (e.g. exercise, computerized cognitive behavioral therapy (CBT) and guided self-help), non-directive counseling, psychological therapies (e.g. CBT or interpersonal psychotherapy), antidepressant medication. Most often may be treated at home but severe cases may need admission	Antipsychotic medication, antidepressant medication, mood stabilizers (e.g. lithium), support and counseling. Often requires admission

Adapted from reference 7

Postpartum psychosis – the most severe forms of postpartum mood disorder have traditionally been labeled as postpartum (or puerperal) psychoses[11]. Although the boundaries of this condition are difficult to define, the core concept is the acute onset of a manic or affective psychosis in the immediate postpartum period; the incidence is approximately 1 in 1000 deliveries. Symptoms are those of severe affective psychosis accompanied by delusions and hallucinations. Mixed episodes, in which manic and depressive symptoms occur simultaneously, are common, and the clinical picture often shows a constantly changing, 'kaleidoscopic', picture. The term 'postpartum psychosis' is usually used to refer to the new onset, although not necessarily the first episode, of a severe affective psychosis in the immediate puerperium. Accordingly, the continuation of a chronic psychosis such as schizophrenia would not be appropriately labeled as a postpartum psychosis.

The classification of episodes of psychiatric disorder in relationship to childbirth is an area that leads to much confusion, both clinically and in research. The classification systems of the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD) do not contain categories for the postpartum conditions described above. They do, however, follow the generally accepted position that postpartum psychosis and depression are not separate nosological entities, but merely represent episodes of mood disorder triggered by childbirth. Consistent with this approach, in

DSM IV a postpartum onset specifier can be employed for mood episodes with onset within 4 weeks of delivery. Despite the postpartum labels not having a place in the classification system, they remain in common use, by both professionals and the lay public. One potential problem, unfortunately, is the ubiquitous use of the term 'postpartum depression' to refer to all forms of psychological distress following pregnancy – from mild and transient mood changes to some of the most severe psychotic conditions seen in psychiatry. This inappropriate usage not only trivializes severe episodes of illness with an underestimation of risk in future pregnancies, but also supports the inappropriate labeling as a psychiatric disorder of a normal mood variation.

WHAT DO WE MEAN BY 'SEVERE MENTAL ILLNESS'?

This chapter focuses on the care of women with pre-existing severe mental illness remembering, of course, that many women experience their first episode of illness in relation to childbirth. Although severe mental illness can be defined in various manners, here it includes women with a history of a psychotic illness such as schizophrenia or those with a severe mood disorder (bipolar disorder or severe recurrent unipolar depression).

WHAT ARE THE ISSUES FOR WOMEN WITH SEVERE MENTAL ILLNESS CONTEMPLATING PREGNANCY?

For women with severe mental illness, pregnancy can present some very complicated issues and necessitate some of the most difficult decisions faced in psychiatry. The questions that women and their partners face include:

- What are the implications of pregnancy and childbirth on the psychiatric illness?
- What is the risk to children of developing psychiatric illness?
- What are the risks and benefits of taking medication in pregnancy?
- How can the risks of becoming unwell be reduced?

Each will be considered in turn.

What are the implications of pregnancy and childbirth on the psychiatric illness?

Although the link between severe psychiatric disorder and childbirth is well established, the increased risk of depressive illness in the postpartum period has come into question following the publication of a number of controlled studies suggesting that depression is no more common in the postpartum period than at any other time in a woman's reproductive life[12–14]. These surprising findings have been attributed to methodological problems in terms of appropriate comparison groups. In particular, the work of Munk-Olsen and colleagues with the Danish psychiatric admission and birth registries demonstrated a 'selection into parenthood' bias, in that women who become mothers are a group at lower risk for psychiatric disorders[15] and studies taking this into account do show an increased risk of depression in the postpartum period, for example an over three-fold increased risk of admission with unipolar depression on postpartum days 31–60 (RR 3.53, 95% CI 2.37–5.05) in the Danish study[15]. In addition, Eberhard-Gran and colleagues[16] found that although rates of depression appeared to be lower in the postpartum period, when other risk factors for depression were controlled for, the risk was actually two-fold higher than at other times.

In contrast, clear evidence supports a specific relationship to childbirth for episodes of severe affective psychosis and for bipolar disorder, in particular[2]. In a large study of the Danish

admission and birth registries that examined over 600,000 pregnancies and their postpartum consequences, women were over 23 times more likely to be admitted with an episode of bipolar disorder in the first postpartum month (RR 23.33, 95% CI 11.52–47.24)[15]. A previous history of admission with bipolar disorder was associated with an even larger increased risk of admission following pregnancy (RR 37.22, 95% CI 13.58–102.4)[17]. Women with bipolar disorder have at least a 1 in 4 risk of suffering a severe recurrence following delivery[18]. Those with a previous history of a severe postpartum episode (postpartum/puerperal psychosis) and those with a family history of postpartum psychosis are at particularly high risk, with greater than 1 in 2 deliveries being affected[18,19] (Figure 1). Postpartum episodes on the bipolar spectrum present a characteristic and close temporal relationship to childbirth. In a study of 111 episodes of postpartum psychosis, 97% of women retrospectively reported the onset of symptoms within the first 2 weeks postpartum, with the majority being on days 1–3[20]. Familial factors have been implicated in the vulnerability to postpartum triggering of bipolar episodes[18]; evidence from linkage studies indicates the possible location of susceptibility genes[21,22].

The risk of admission in the postpartum period also appears to be higher in women with a history of schizophrenia, with Scandinavian register studies documenting increased postpartum admission rates[15,23]. Indeed, one study from the Swedish register found 15% of women with a previous diagnosis of schizophrenia were admitted in the postpartum months[23]. However, the association with childbirth is not as dramatic as it is for bipolar disorder nor does it have such a close temporal relationship to delivery (Figure 2). For bipolar disorder, the risk is for the new onset of an episode of severe affective psychosis. In contrast, women with schizophrenia may be admitted for different reasons, due to difficulties in parenting for example, or owing to the influence of more longstanding psychotic symptoms.

In summary, although the postpartum may be a period of risk for women with a wide variety of psychiatric disorders, it is women with a history of bipolar disorder who are at a particularly high risk of a severe recurrence.

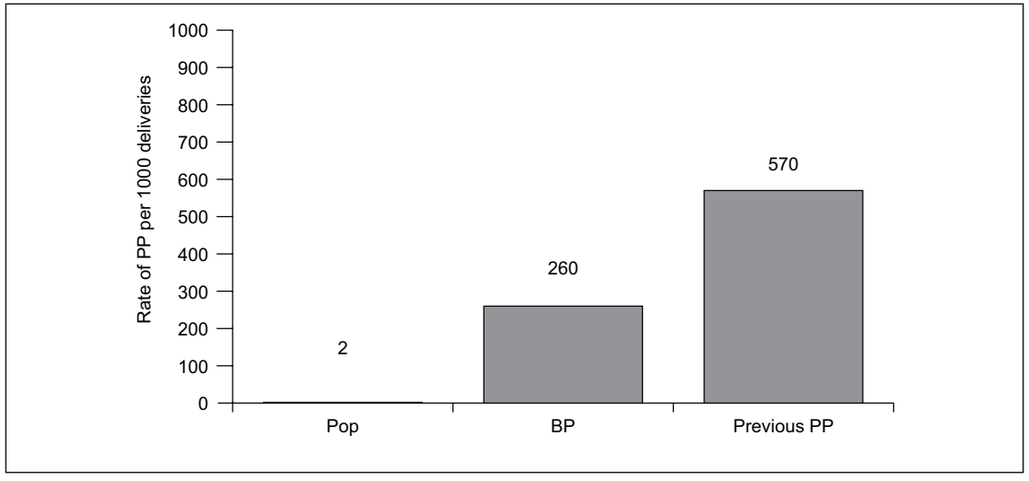

Figure 1 Rates of postpartum psychosis (PP) per 1000 deliveries for women in the general population (Pop), bipolar women (BP) and women who have suffered a previous episode of bipolar affective puerperal psychosis (previous PP). Data from references 18 and 19

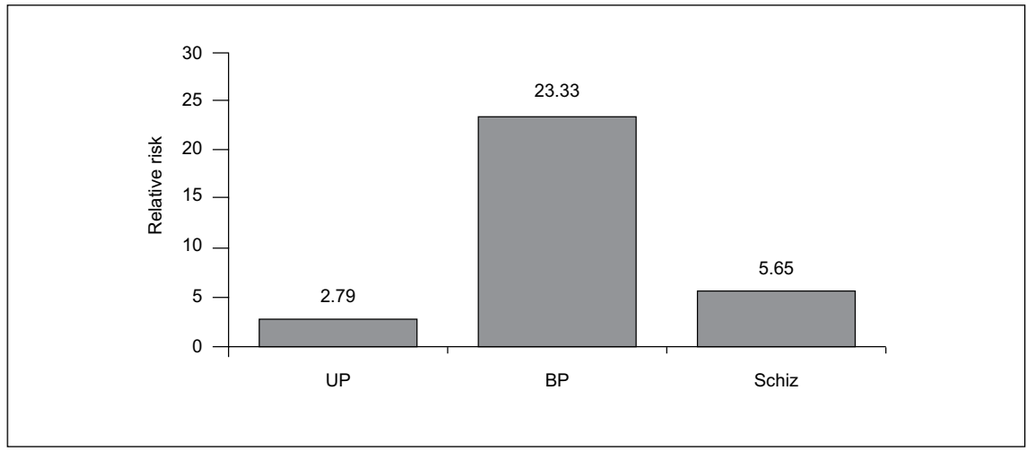

Figure 2 Increased risk of admission following delivery compared to at other times in a woman's life for women with a history of unipolar depression (UP), bipolar disorder (BP) and schizophrenia (Schiz). Data from reference 15

What is the risk to children of developing psychiatric illness?

In addition to considering the effects of pregnancy and childbirth on a woman's illness, families with a history of severe mental illness have another issue to consider when starting a family. It has long been obvious that psychiatric disorders run in families, and family, twin and adoption studies have confirmed a high levels of hereditability for many severe mental illnesses[24]. Prospective parents may have experienced illness themselves or witnessed first hand the suffering of a family member and be concerned about passing on this risk to their children; on occasion, the risk to offspring may be the main concern of women seeking advice. It is usual, however, for prospective parents to overestimate the risk to their children, and it is generally possible to reassure women and their partners.

As is typical for a complex genetic disorder, the risk falls off quickly with the distance from the affected relative. Couples who are concerned, therefore, about a history in their families but who have remained well themselves can be reassured that for them the risk is low. For women or their partners who have suffered episodes of illness themselves, on the other hand, it is still likely that the true risk is lower than they imagine. Table 2 gives the approximate lifetime risk of mood disorder for children of a parent with bipolar I disorder. There are few data to give meaningful estimates for more distant family members, but available evidence suggests rates that are between those for first degree relatives and the general population. These figures can be used as very approximate 'order of magnitude' guides and, with appropriate caveats, can be used to provide information to women and their partners.

What are the risks and benefits of taking medication in pregnancy?

For women with a history of severe mental illness, the biggest issues faced when starting a family often relate to medication. Decisions are made all the more problematic by the lack of data on the reproductive safety of many of

Table 2 The lifetime risks of mood disorder for the offspring of parents who suffer with bipolar I disorder. There are few data to give meaningful estimates for more distant family members but the available evidence suggests rates that are between those for first degree relatives and the general population

Relationship to child	*Lifetime risk of bipolar I disorder*	*Lifetime risk of major depression*
General population	0.5–1.5%	5–10%
Bipolar disorder in mother, father or sibling	4–9%	8–20%

Modified from reference 24

the medications commonly used to treat psychiatric illness. It is disappointing that even for a medication such as lithium that has been in use for over half a century, the sum total of the world literature is not even 200 prospective cases of exposure in pregnancy. In contrast, the situation is certainly better for medications used in psychiatry and additionally used in the treatment of epilepsy, but there are potentially important differences in how medications are prescribed in other disorders, for example in dose and in the particular combinations with other medications.

It is clearly not appropriate in a book such as this to make definitive statements about what are the safest and the most problematic medications to use in pregnancy, as the evidence base is constantly changing, and pronouncements such as these can become dangerously out of date very quickly. Rather, it is more appropriate to deal in general principles that should guide care.

Principles of drug management

There is no right or wrong answer to the question of whether an individual woman should continue a particular medication throughout her pregnancy. Although some medications clearly carry a higher risk than others, sodium valproate being a prime example, each decision should involve consideration of a complex balance of risks and benefits.

The risks involved in continuing specific medications include teratogenicity, toxicity or withdrawal symptoms in the newborn as well as the less certain risks of long-term developmental and cognitive problems in children exposed to the medication *in utero*. Weighed against these risks, however, are the risks of untreated psychiatric disorders, including the risk of a severe recurrence of illness. A range of studies implicate psychiatric disorder as having important consequences on pregnancy, birth weight and gestational age at delivery[25]; in addition, both animal and human literature document the detrimental effect of stress during pregnancy on the fetus[26]. Furthermore, concerns exist that having a severe episode of psychiatric illness at this time may impact on mother–infant attachment with possible longer-term effects on the child[27].

Compelling evidence also suggests that women with unipolar and/or bipolar disorder who discontinue medication in order to conceive risk a severe recurrence of illness. In a naturalistic study of 89 women with bipolar disorder throughout pregnancy, recurrence risk was two-fold greater among women who discontinued versus those who continued mood stabilizer treatment, median time to first recurrence was more than four-fold shorter, and the proportion of weeks ill during pregnancy was five times greater[28]. A similar difference in recurrence risk has been described in women with unipolar depression. Of 201 euthymic women with a history of major mental disorder (MDD), 68% of those who discontinued

their antidepressant experienced a recurrence in pregnancy compared to 26% of those who remained on their medication[29]. In the latter study, however, it is important to note that the women studied had a severe form of unipolar depression (mean duration of 15.4 years with 44% having had five or more episodes), and the same recurrence risks may not apply to the many women with a less severe mood disorder who become pregnant on antidepressant medication.

As a general principle, some women will clearly be looking for guidance, and professionals should not shirk their responsibility to advise on appropriate options. Fully documenting the nature and extent of any discussion is clearly important.

When it comes to the decision about which medication to use, it is important to consider drugs with the best evidence of reproductive safety. However, an individual woman's history of response to various medications is clearly of vital importance. Polypharmacy should be avoided if possible, and the lowest dose of any medication should be used for the shortest period. However, if the fetus is to be exposed to a medication in pregnancy, it would not be sensible to use it in a dose too small to be effective or to stop medication too soon, thus leading to a high risk of relapse.

Inadvertent conception on medication

In an ideal world, all women with a history of severe mental illness would seek advice on a prospective pregnancy at the preconception stage, ideally a number of months or even years before pregnancy is desired, thus giving plenty of time to explore alternative medication options prior to conception. This situation, however, remains unusual. In addition, the regularly estimated 50% of pregnancies that are unplanned may even be higher in women with severe mental illness. Clearly, many women with mental illness will be faced with making difficult decisions in early pregnancy about continuing medication treatments when exposure of the fetus has already occurred.

Decisions regarding the final choice of possible options may be agonizing for the patient and difficult for the health care professional. Possibilities include stopping a medication altogether, although an abrupt discontinuation may lead to withdrawal phenomena or withdrawal precipitation of an episode; switching to a drug with greater evidence of reproductive safety, although this often involves exposure to two medications and the second drug may not have the efficacy of the original; and, finally, continuing the current medication with close monitoring of the fetus and the neonate. Clearly, there are no easy answers, and again a full and individualized risk–benefit analysis is important and should be meticulously documented in the patient record which should also state that the analysis had been accepted and understood by the patient.

How can the risks of becoming unwell be reduced?

As discussed above, women with bipolar disorder are at particularly high risk for severe postpartum episodes[2]. For women with a bipolar history, additional factors that increase risk include having experienced a previous episode of severe illness in relationship to childbirth[19] and having a first degree relative who has experienced an episode of postpartum psychosis[18]. Unfortunately, women at high risk according to these criteria may be well, not in contact with mental health services and may fail to recognize the seriousness of their situation. It is clear, therefore, that all antenatal women should be asked about the above risk factors and protocols should be put in place to ensure that women at potential risk receive a formal risk assessment and management plan[2,30]. How screening and risk management is delivered

may differ considerably according to local circumstances, but all women with a history of bipolar or severe postpartum episodes should be identified by antenatal services.

The risks of illness following childbirth should be discussed with all women with a history of severe mental illness in the childbearing years, and the need for contraception and the importance of seeking help if contemplating pregnancy (or if unexpectedly becoming pregnant) emphasized. As a large proportion of pregnancies are unplanned, all women with childbearing potential merit thorough consideration of potential pregnancy when making decisions about initiating a given medication. This fact lies behind the widespread recognition that, due to its particular teratogenic and developmental effects, sodium valproate should not be used in women in their reproductive years if it can be avoided[30].

Decisions about continuing or stopping medications prior to or during pregnancy are difficult and should be the result of a detailed and individualized cost–benefit analysis. As noted above, stopping medication is not without its own risks[28]. No universal recommendations can be made, and the decision ultimately must rest with the woman and her family. Stopping medication should always be a carefully considered decision and never a reflex response; on the other hand, the decision to start medication for women who become symptomatic in pregnancy or when breastfeeding must be the result of weighing the potential risks from taking medication and the risks posed by the illness itself.

For women with a history of mental illness, attention should also be given to the wide range of additional factors that can influence the health of the pregnancy and the newborn. It is easy to focus exclusively on medication and neglect other issues such as drug and alcohol usage, smoking, diet, obesity and routine antenatal care, including folic acid supplementation prior to the onset of pregnancy and the need for monitoring throughout the gestation. For women taking anticonvulsants that deplete folic acid, a high dose (4–5 mg/day) is a sensible option to consider as opposed to the usual dose of 400 μg. In either situation, the patient must be carefully advised that the neural tube closes by the 28th day of gestation and that initiation of supplementation after that date is without effect. Therefore, patients with a history of mental illness who *might* become pregnant are well advised to supplement as a routine health care measure.

For women at risk, perhaps the most important aspect of management is to maintain close contact with their health care professionals and remain under review during the perinatal period. It is also important to address other avoidable factors that may increase risk such as decreasing general levels of stress, for example, and paying attention to sleep patterns in late pregnancy and the early postpartum weeks. Finally, for women who have discontinued medication during or prior to pregnancy, it is appropriate to consider the introduction of prophylactic medication in the immediate postpartum period. Some evidence exists for the use of lithium in this context[31], but the few studies conducted have been open and retrospective, and there are practical problems with obtaining therapeutic levels quickly to cover the period of risk. These issues have led some psychiatrists to use typical or atypical neuroleptics as prophylaxis and, despite some anecdotal reports of success with this strategy, there are few data in the literature.

EXPLAINING RISK – HOW DO WE EXPLAIN THE COMPLEXITIES OF THESE RISKS AND BENEFITS?

First, it is important to consider the strength of the available evidence. Is there a real risk of teratogenicity? For example, how consistent is the evidence of risk across a range of studies employing differing methodologies? Moreover, although seemingly exact figures

are often given for the risk of particular medications causing malformations, it is important to consider the accuracy of these estimates. With lithium, for example, although a 7% malformation rate is often quoted, the confidence intervals around this estimate are very wide and it is important to convey this uncertainty.

Another major consideration is how to determine what level of information women want or are able to assimilate. Health care professionals need to be sensitive to differences between individual women and, wherever possible, individualize the information as well as the manner in which it is delivered. Finally, what language should be used in our explanations – how do we frame risk? The same data, delivered in a variety of manners, can confer very different messages. Health care professionals must be aware of their own biases and of the temptation to frame the information provided in a way that results in the decision they believe is correct.

Undoubtedly, this whole area is difficult and one in which more research is needed. Regardless, some general guidelines are appropriate. Information should be provided in a user-friendly manner. Changes in risk should be given in absolute rather than relative terms with a uniform denominator[30]. For example, patients are better informed when they are told that risk is increased from 1 in 100 to 3 in 100 rather than risk is increased three fold. Using visual aids, providing written (preferably individualized) information and even audiotaping advice have all been recommended[29].

Because any decision(s) is complex and based on a difficult balance of risks and benefits, a woman may require time to process the information and discuss her thoughts and feelings with her partner, friends and family. These are not discussions that can be fit into a few minutes at the end of a consultation; where a specialist opinion is available (specialists in perinatal/reproductive psychiatry are increasingly found in many countries), women should be referred as early as possible to discuss their options.

SUMMARY AND CONCLUSIONS

For women with a history of severe mental illness, pregnancy raises a number of difficult issues. Severe recurrences are common in relationship to childbirth, and for women with bipolar disorder the risk is very high. Many medications used to keep women well are of known or potential teratogenicity, but stopping medication may be associated with a very high risk of disorder recurrence. At least 50% of pregnancies are unplanned which means that these are issues that must be discussed with all women with reproductive potential. Clearly, the earlier potential pregnancy is considered the better; many months or even years may be required to explore alternative treatment options prior to pregnancy. Finally, although there is a case to be made for perinatal psychiatry specialists and services, mental health is an important consideration for all professionals who come into contact with women in the preconception, antenatal and postpartum periods.

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SECTION 2
Infectious conditions

14

Tuberculosis in pregnancy

Archana Gorty and Muktar Aliyu

BASIC EPIDEMIOLOGY OF TUBERCULOSIS

According to World Health Organization data, 9.2 million incident cases and 1.7 million deaths were attributed to tuberculosis in 2006, the overwhelming majority of which affected individuals residing in developing nations[1]. A staggering one-third of the world's population is estimated to be infected with tuberculosis. Of those infected, 5–10% progress to active tuberculosis (TB) in their lifetime, with HIV-positive individuals carrying an even higher risk of progression to active disease[2]. Worldwide, approximately 3 million women become afflicted with TB each year and 750,000 die, rendering tuberculosis one of the leading infectious disease causes of death in women[3].

In the UK, the number of tuberculosis cases declined until the mid-1980s, but began rising again in the early 1990s. In 2006, there were 8497 cases of TB reported (14 per 100,000). The London metropolitan area accounted for 40% of these cases (44.8/100,000)[4]. This represents a rise from 2002, when 6638 cases were identified. Approximately 350 people die annually from TB in the UK[5]. In terms of demographics, 2003 data reveal that the TB incidence in London was 11 times higher for foreign-born individuals (83% of reported cases) than for UK-born individuals[6]. Of equal importance, between 1998 and 2005 rates of TB cases resistant to isoniazid increased from 5% to 7%, those resistant to rifampicin from 1% to 1.2% and those with multidrug resistance from 0.8% to 0.9%[7].

These data mirror similar figures from the USA, where the years 1985–1992 witnessed a rise in TB rates, which has been variably ascribed to the coincident HIV epidemic, degradation of public health support for TB eradication, homelessness, alcohol and drug use, and increased immigration from countries with endemic tuberculosis[8] (Figure 1). Foreign-born cases represented 58% of total reported TB cases in the US in 2006[9,10]. From the general cohort of infected individuals, 116 multidrug-resistant TB (MDRTB) and four extensively drug-resistant TB (XDR) individuals were reported to health authorities in 2006[9,10]. The current incidence of TB infection in pregnant women in the US ranges from 0.1 to 1.9%, but this percentage is predicted to rise, given the general increase of TB incidence. The rate of new cases in women attains its zenith between the ages of 25 and 34[11].

DEFINITIONS OF TUBERCULOSIS TERMS AND ACRONYMS, BASIC MICROBIOLOGY AND PATHOPHYSIOLOGY

Mycobacterium tuberculosis (MTB) is a small, aerobic bacillus within the family *Mycobacteriaceae*, which also includes *Mycobacterium bovis*, *Mycobacterium africanum* and *Mycobacterium microti*. All species possess cell walls laden with lipids and waxy substances, which enable

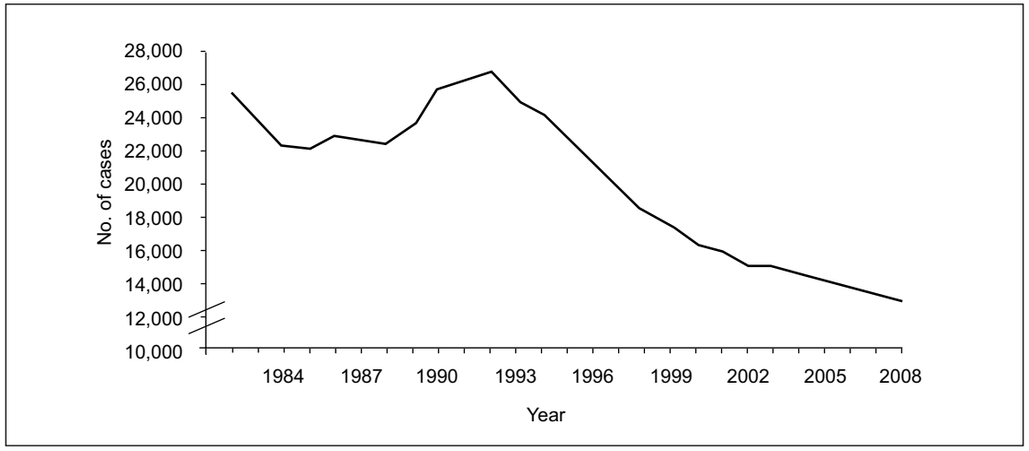

Figure 1 Reported TB cases in the USA for 1982–2008[9]

them to elude typical Gram stain. The term acid-fast arises from observations pertaining to two different commonly utilized staining mechanisms: carbol fuchsin (Ziehl-Neelsen and Kinyoun) and a fluorochrome method which uses auramine-O or auramine-rhodamine. Once stained, bacilli retain their color even after an acid-alcohol wash, and are thus referred to as 'acid-fast'[12,13].

Transmission occurs when infected individuals aerosolize organisms during coughing, sneezing, singing, or speaking; respiratory droplets persist in the air for hours. Infectious aerosolized particles lodge in the host's alveoli, where alveolar macrophages encounter them and they undergo phagocytosis. After initial infection, the lifetime risk of progression to active disease is 10%, with a 5% risk of progression within the first 2 years. Host factors such as age, comorbid conditions, especially those affecting the immune system, and nutritional status all influence the probability of progression. Mycobacteria somehow evade death within macrophages, replicate within these cells, and spread throughout the lymphatic system to other parts of the body. In individuals with normally functioning cell-mediated immunity, macrophages attract T lymphocytes, which then work in concert to form granulomas to contain further spread. This response typically occurs over 2–8 weeks, and is the basis of the tuberculin skin test (TST). Antibodies are also formed to MTB, but do not appear to confer protection[13]. Activated T lymphocytes secrete interferon γ, which serves as the immunologic rationale for the interferon γ release assay (IGRA); QuantiFERON (Cellestis Ltd, Australia) and ELISpot (Oxford Immunotec Ltd, UK) being two common blood tests which help detect latent tuberculosis infection[14]. The Mantoux skin test is the oldest test in continual use, whereas the blood tests are relative newcomers (Table 1).

Primary infection occurs when MTB enters a susceptible host, a process resulting in three potential outcomes:

1. Latent tuberculosis infection (LTBI), which refers to an asymptomatic and non-infectious state after the host has mounted an effective granulomatous response, successfully sequestering the organism, and one that satisfies the conditions of having either a positive TST or QuantiFERON test, a negative chest X-ray and no evidence for active TB disease either symptomatically (i.e. night sweats, weight loss, prolonged cough, hemoptysis) or by laboratory evaluation (i.e. positive sputum cultures)[17];
2. Primary tuberculosis, which refers to active disease within the first 2 years of infection;
3. Reactivation disease, which signifies active disease after a period of latency beyond 2 years.

Table 1 Tuberculosis tests

	Specificity (%)	*Sensitivity* (%)	*Affected by BCG vaccine*	*Mechanism*
Tuberculin skin test	97*	77**	Yes	Measures amount of skin induration based on cutaneous delayed-type hypersensitivity response to purified protein derivative
ELISpot	93†	90†	No†	Measures the number of IFNγ-producing T cells in reaction to the antigens ESAT-6 and CFP-10 produced by MTB, and not in the BCG vaccine
ELISA	96†	70†	No†	Measures the serum concentration of IFN-γ produced by T cells in reaction to the antigens ESAT-6 and CFP-10 produced by MTB, and not in the BCG vaccine

BCG, Bacille Calmette-Guerin; ESAT-6, early secretory antigen target-6; CFP-10, culture filtrate protein 10; MTB, *Mycobacterium tuberculosis*; IFN, interferon

*In non-BCG vaccinated individuals. **From Pai *et al*.[15] †From Lalvani *et al*.[16]

MDRTB denotes TB which is resistant to the two first-line drugs, isoniazid and rifampicin, while XDR refers to MDRTB which is also resistant to any one of the fluoroquinolones as well as one of the intravenous second-line medications which include amikacin, kanamycin or capreomycin[18].

Compared to the general public, signs and symptoms are no different for pregnant women, but diagnosis is often delayed. Manifestations of active TB depend on the site, which for most people is pulmonary, although the bacterium may attack any part of the body, including the lymphatic, genitourinary (especially damaging in females), musculoskeletal, central nervous, gastrointestinal and cardiac systems. Manifestations of pulmonary TB include cough, weight loss, fever, fatigue and malaise, hemoptysis, night sweats and chest pain. The non-specific nature of these symptoms, as well as the often ill-informed reluctance to perform radiographic testing in pregnancy, presents a diagnostic challenge to physicians. For these reasons, health care providers must be vigilant to consider this diagnosis in pregnant patients[19].

TUBERCULOSIS AND PREGNANCY

Opinions regarding the effects of tuberculosis on pregnancy, and conversely, of pregnancy on the course of tuberculosis, have varied greatly throughout history. In the era of Hippocrates,

pregnancy was thought to have a salutary effect on tuberculosis, this perspective being in diametric opposition to that of the early 20th century when professionals actually recommended therapeutic abortions if pregnancy and tuberculosis diagnoses coincided. Current medical opinion holds that pregnancy and TB do not affect each other's course, but that active tuberculosis has adverse obstetrical and neonatal outcomes[19]. One prospective cohort study compared pregnant women with TB (subdivided into those treated early or before pregnancy and those treated in the second or third trimester) to pregnant, non-tuberculosis infected women, and found that pulmonary TB was the most common manifestation in pregnancy. Furthermore, the relative risk of obstetrical morbidity (defined by the authors as 'the presence of any complication during pregnancy attributed directly or not to the infectious disease') in TB-infected patients was three times the risk of uninfected individuals; this risk increased when treatment commenced later in the pregnancy[20]. Major complications experienced by women in this study included preterm labor, pre-eclampsia, premature rupture of membranes and fetal growth retardation. Average birth weight was 200 g lower for infants whose mothers had TB versus controls[18]. Other studies corroborate these findings. In one series, active pulmonary TB was associated with prematurity, fetal growth retardation, low birth weight and increased perinatal mortality among infants of mothers with TB as compared to infants of healthy women[21]. Another prospective cohort study that examined the effects of extrapulmonary TB (representing about 10–27% of TB cases), found that tuberculous lymphadenitis had no effect on pregnancy or perinatal outcome, but women with other-site extrapulmonary disease suffered more antenatal hospitalizations, and had babies with lower Apgar scores and lower birth weights compared to non-infected controls[22]. Other studies have also documented adverse neonatal outcomes. One series demonstrated a 23% morbidity rate among children born to TB-infected mothers versus 3.8% in the control group, including higher incidences of prematurity, perinatal mortality and low birth weight among the TB group. Risk factors included maternal pulmonary disease and late start of treatment[23]. Other considerations include the fact that congenital tuberculosis is a rare but serious complication of maternal TB, and the presence of genitourinary TB remains an important cause of female infertility, especially in developing countries. In summary, active tuberculosis produces deleterious effects on the mother as well as on the newborn, and merits prompt diagnosis and treatment.

TUBERCULOSIS SCREENING

The Health Protection Agency in the UK recommends targeted screening of pregnant women for TB; for instance, for those who have recently been exposed to tuberculosis (occupational or household contacts), or for those who are HIV positive. Screening should then proceed with determination of Bacille Calmette-Guerin (BCG) vaccination status, tuberculin testing, interferon γ blood tests and/or chest radiography if indicated[24]. Chemoprophylaxis should commence if a pregnant woman is a close contact of a known active TB case and has reactive skin or blood tests, with a negative chest X-ray. A Mantoux TST is considered positive with induration of 6 mm or more[25]. The recommended treatment regimen is 6 months of isoniazid plus pyridoxine.

Another question to be considered is provision of the BCG vaccine as a preventive measure. Because BCG is a live attenuated vaccine, it should not be administered during pregnancy. The 2005 UK Department of Health guidelines recommend that all infants (0–12 months) receive the BCG vaccine as soon as possible (preferably prior to hospital discharge) if they reside in areas where TB

incidence is 40/100,000 or higher, or they have a parent or grandparent whose country of origin carries a TB incidence of 40/100,000 or higher[26].

Because most cases of active TB in the US arise from LTBI patients, the joint Centers for Disease Control and Prevention (CDC) and American Thoracic Society (ATS) guidelines recommend targeted testing for tuberculosis among high-risk individuals as a strategic method to reduce prevalence[27]. The CDC notes cut-offs of >5 mm induration, >10 mm induration and >15 mm induration in the interpretations of the TST, depending on the risk factors of the tested individual (Table 2)[28].

According to the National Institute for Clinical Excellence (NICE), the probability of evolution to active tuberculosis in a latently infected individual is enhanced by HIV positivity, injection drug use, solid organ transplantation, jejuno-ileal bypass or gastrectomy, presence of a hematological malignancy, chronic renal failure or on hemodialysis, receiving antitumor necrosis factor (TNF)-α treatment or history of silicosis[25]. The US guidelines have similar criteria for assessing risk of progression to active TB and, in addition, include age under 20 years, abnormal or fibrotic lung lesions, underweight by 10% or more of ideal body weight, diabetes mellitus, prolonged corticosteroid therapy, and head and neck cancers[27,28].

Table 2 Recommendations for targeted tuberculin testing

High risk (+PPD = 5 mm)
HIV positive
Contacts of TB patients
Fibrotic changes on chest radiograph
Organ transplantation patients
Persons on prolonged corticosteroid therapy
Moderate risk (+PPD = 10 mm)
Recent immigrants from high prevalence countries
Injection drug users
Homeless persons
Resident or employee of high-risk congregate setting
Mycobacteriology laboratory employee
People with certain clinical conditions (silicosis, diabetes mellitus, renal failure, underweight, gastrectomy, certain cancers)
Children younger than 4 years of age
Infants, children or adolescents exposed to high-risk adult
Low risk (+PPD = 15 mm)
Testing not recommended

PPD, purified protein derivative. Adapted from Bergeron *et al*.[28]

Treatment of LTBI represents one of the chief means of TB control in low-TB incidence nations. Although the BCG vaccine, a live attenuated strain of *M. bovis*, is available in many nations around the world, it is not an approved method of TB control in the US. It is, however, used with varying degrees of success for primary prevention and to mitigate against disseminated or devastating disease in many other parts of the world, particularly in children, including in the UK[12]. As previously mentioned, the BCG vaccination is not given to pregnant women, but may be considered in (1) neonates born in an area with TB incidence of >40/100,000 or with a parent or grandparent born in a high-incidence country or with a family history of TB within the past 5 years; (2) infants and children (older than 4 weeks and younger than 16 years) who are at increased risk (would qualify for neonatal vaccine) and are Mantoux negative; (3) selected new entrants to the UK (from high-incidence nations and without previous vaccination as noted by history and/or scar); (4) health care workers (without prior history of BCG vaccination, and who are Mantoux or interferon γ negative); (5) contacts of people with active TB, and others at increased risk of contracting TB (e.g. working with prisoners or in nursing homes)[25].

Recommended screening for TB begins with the TST, 0.1 ml of 5 units of purified protein derivative (PPD) injected intradermally on the

volar aspect of the forearm and read 48–72 hours later[28]. If used, this test should be performed as early in the pregnancy as possible or, in high-risk populations, preconceptionally. The biological basis of the TST is a delayed-type hypersensitivity reaction to antigenic moieties derived from the mycobacterium. Previous exposure to the BCG vaccine may confound visual test interpretation, however, by producing a potentially false-positive reaction. Fortunately, the newer IGRAs do not cross-react with previous inoculation with the BCG vaccine; on the other hand, their use has not been extensively evaluated in pregnant populations[29,30]. The joint 2008 CDC/ATS statement on diagnostic evaluation also underscores the exigency of evaluating for active TB if a positive reaction is obtained. A recent prospective study to evaluate a newer T cell-based IGRA called ELISpot-PLUS, found the ELISpot-PLUS assay to be more sensitive than the standard ELISpot test, and was particularly effective in helping to rule out latent or active TB if used in conjunction with the TST when a moderate to high pretest probability exists[31]. In general, the IGRAs have excellent specificity, and results are not confounded by previous BCG vaccination; sensitivity is not quite as high, but the T-SPOT appears to have greater sensitivity than either the TST or the QuantiFERON tests[31,32].

DIAGNOSIS AND TREATMENT

Health care professionals caring for pregnant women with TB ideally should consult with a knowledgeable pulmonary or infectious disease colleague for advice and guidance, especially if comorbid diseases and conditions exist or are suspected to exist, such as HIV infection or MDR or XDRTB. Tripathy and Tripathy[33] concluded in a prospective study that no statistical differences existed between pregnant women divided into TB-positive women who received antituberculosis chemotherapy throughout pregnancy and non-TB infected same sex controls in terms of outcomes of gestational duration, occurrence of preterm labor, or congenital anomalies of their babies[33]. The CDC concurs that most first-line agents for tuberculosis are safe to use during pregnancy, even though they do cross the placenta.

Directly observed therapy (DOT) is an important component of treatment regimens in the US and India; however, in the UK, DOT is not usually required for most standard cases of active TB unless the risk assessment for treatment adherence reveals homelessness, or history of previous non-adherence to therapy[25]. DOT is a widely recognized strategy of TB management whereby health workers directly observe patients as they take their medication. This strategy increases adherence and reduces the likelihood of emergence of drug-resistant forms of *Mycobacterium tuberculosis*. If the TST or IGRA is positive, a meticulous history should be performed, specifically assessing for BCG vaccination history, symptoms of active TB, past or present contacts of infectious TB patients, previous PPD history (especially if negative within the last 2 years), and indicators of immune dysfunction. If suspicious symptoms or comorbid immunosuppressing conditions exist, a shielded chest X-ray should be performed; otherwise, shielded radiographic evaluation can be deferred until the second trimester. A positive chest X-ray prompts the need to examine three sputum samples collected at separate times for acid-fast bacilli smear, culture and susceptibility testing[28].

LATENT TUBERCULOSIS INFECTION

Pregnant women diagnosed with LTBI are at high risk of developing active TB, especially if they are HIV positive, have had contact with active TB cases, or reveal new PPD positivity within the past 2 years. Such women should begin treatment in the first trimester in any of the aforementioned circumstances[28].

Otherwise healthy women may wait until the postpartum period to commence their treatment of LTBI. Some experts advocate treating LTBI during pregnancy for all patients regardless of risk of progression to active TB, asserting that for some higher-risk women (homeless, immigrants from endemic areas, low socioeconomic status, etc.) pregnancy represents the only encounter with and opportunity for medical care. This statement is true both in resource poor and in developed countries. Treatment should be viewed as a critical means of preventing active TB in vulnerable populations and as a means to contain further spread in the communities wherein these women and their babies reside[28,34]. A cost–benefit analysis conducted by Boggess *et al*. described favorable economics for antenatal treatment of LTBI even with the increased need for hepatotoxicity monitoring related to isoniazid[35]. Regardless of these considerations, presently both the CDC and the American College of Obstetricians and Gynecologists (ACOG) recommend targeted testing for TB only in high-risk populations, and, unless compelling reasons exist (HIV infection, recent TB infection), delaying LTBI treatment until 2–3 months postpartum. This position is mostly in deference to fears of exposure to any medications during pregnancy.

In the UK, isoniazid is considered safe for treatment of latent TB during pregnancy, although the general reluctance to prescribe medications during gestation is acknowledged; treatment may be delayed until the postpartum period unless the woman is HIV positive or has had recent contact with active TB cases. Bothamley cites the East European Prevention Trial, whereby isoniazid was used for chemoprophylaxis, and determined that the risk attributed to isoniazid was two orders of magnitude less than the risk of TB on the pregnancy[36]. A common regimen for treatment of LTBI consists of isoniazid plus pyridoxine for 6 months[36]. Bothamley recommends that baseline liver function testing be performed before initiating isoniazid therapy, repeated every 2 weeks for the first 8 weeks of therapy (or weekly if chronic liver disease is present), and continued monthly for the remainder of pregnancy and certainly if symptoms such as fever, malaise, anorexia, or jaundice occur. Isoniazid and other hepatotoxic medications such as rifampicin and pyrazinamide should be discontinued if liver function tests exceed 3–5 times the upper limits of normal[36]. The CDC recommends isoniazid daily or twice a week for 9 months for women at high risk of developing active disease. Pregnant women on isoniazid should receive pyridoxine supplementation to diminish the risk of peripheral neuropathy[27]. Baseline liver function testing is recommended in pregnant women receiving isoniazid, and routine clinical and laboratory monitoring during therapy should be considered. It is recommended to discontinue isoniazid if liver function enzymes exceed three times the upper limits of normal in symptomatic patients, or five times the upper limits of normal in asymptomatic patients[11].

ACTIVE TUBERCULOSIS

The CDC states that untreated active TB imperils a pregnant woman and her baby more than the treatment itself[29]. Medications contraindicated in pregnancy include streptomycin (concerns of fetal hearing loss); kanamycin and amikacin (risks of nephrotoxicity and congenital hearing loss); capreomycin (risks of nephrotoxicity and congenital hearing loss); and, finally, the fluoroquinolones (due to teratogenic effects). In the US, relative contraindications to PZA (pyrazinamide) exist mostly due to a dearth of evidence regarding its use[30].

Treatment is divided into an initial or intensive phase followed by a continuation phase. The initial phase is intended to kill actively replicating and semidormant bacteria. Three or more drugs are used to help guard against the emergence of resistant organisms. In

non-pregnant individuals, the initial phase typically is 2 months in duration, and consists of a four-drug plan consisting of isoniazid, rifampicin, pyrazinamide and ethambutol. The continuation phase, on the other hand, consists of isoniazid and a rifamycin product daily or intermittently for the remaining 4–7 months. The choice of drugs and length of administration depend on organism susceptibility, site and severity of disease[37]. In the UK, standard treatment for TB, consisting of isoniazid and rifampicin for 6 months, with pyrazinamide and ethambutol for the first 2 months, may be given throughout pregnancy. Whereas daily or intermittent (three times a week) treatment is acceptable, intermittent treatment is cheaper and also allows for supervised therapy. Twice weekly regimens are not recommended because adverse effects from rifampicin may become more evident[36]. The UK regimen is a departure from therapy in the US, where pyrazinamide is relatively contraindicated. The CDC guidelines state:

> 'The initial treatment regimen should consist of INH [isoniazid], RIF [rifampicin], and EMB [ethambutol]. SM [streptomycin] should not be substituted for EMB. Although PZA [pyrazinamide] is recommended for routine use in pregnant women by the WHO[37] and the IUATLD[38], the drug has not been recommended for general use in pregnant women in the United States because of insufficient data to determine safety…If PZA is not included in the initial treatment regimen, the minimum duration of therapy is 9 months. Pyridoxine, 25 mg/day, should be given to pregnant women who are receiving INH…INH, RIF, and EMB cross the placenta, but none has been shown to have teratogenic effects[39]. SM (streptomycin), the only antituberculosis drug documented to have harmful effects on the human fetus, interferes with development of the ear and may cause congenital deafness…The fluoroquinolones have been associated with arthropathies in young animals; therefore, they should be avoided if possible in pregnant women…In general, administration of antituberculosis drugs is not an indication for termination of pregnancy...'[30].

BREASTFEEDING

Breastfeeding may continue in women being treated for LTBI. First-line agents do enter breast milk, but have not been found to produce toxicity in the newborn[30]. Mothers with active TB who may still communicate the disease should not remain in direct contact with their infants to reduce the risk of spread. MTB bacilli do not enter breast milk, and such women may pump their milk to be fed to their infants, unless the mother possesses a tuberculous breast lesion. If a tuberculous breast lesion does exist, however, the mother may pump and discard the milk to maintain her supply until the lesion heals. When the mother is no longer considered infectious (amelioration of signs or symptoms of active disease, has been on effective therapy for at least 2 weeks, and repeat sputum smear is negative), she may resume direct breastfeeding of her child[41].

MULTIDRUG RESISTANT TUBERCULOSIS AND HIV INFECTION

MDRTB necessitates treatment using second-line drugs for which there is limited clinical experience. One study found no significant evidence of toxicity in children either congenitally or at long-term follow-up (average age 3.7 years) with use of second-line drugs[42]; another revealed no obstetrical complications or congenital TB transmission in a series of pregnant women treated for MDRTB[43]. This suggests that MDRTB may be successfully treated during pregnancy without significant harm to mother or child, and without requiring recommendation of a therapeutic abortion[43].

Any tuberculosis-positive patient should be tested for concurrent HIV infection. HIV greatly increases the risk of progression to active TB. HIV is believed to complicate tuberculosis treatment during pregnancy primarily by drug interactions between HIV and tuberculosis medications, especially rifampicin, which induces hepatic drug metabolism[35].

In conclusion, TB remains an increasingly common infectious disease and a major cause of mortality and morbidity among pregnant women worldwide. Diagnosis of TB in pregnancy is frequently delayed, and a high index of suspicion is often required to detect it. Nevertheless, pregnancy can be an important opportunity for identification and treatment of TB. The authors wish to emphasize that any health care provider who undertakes treatment of pregnant women with MDR or XDRTB and/or HIV should do so in close collaboration with experts in pulmonary and infectious diseases.

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15

Preconception advice and the optimal management of HIV infection for couples planning pregnancy

Anne Edwards and Yetunde Okunwobi-Smith

The two major aims of preconception care are to identify risks and to take measures to reduce these risks. In terms of HIV, before the development of antiretroviral therapy (ART) the risk of mother to child viral transmission ranged from 15 to 40%[1]. Of equal importance was the high mortality associated with HIV which meant that uninfected children were likely to be left motherless in the first few years of life[2,3]. Faced with these statistics, most physicians actively discouraged HIV positive women from becoming pregnant. The development of ART, however, means that with optimal medical care HIV can be viewed as a chronic infection with a life expectancy approaching normal[4–7]. Unfortunately, this reality is not yet the case in resource limited settings[8].

The use of ART in pregnancy has changed the transmission risk from 15–40% in the untreated woman to less than 2%[9]. Given up to date advice on pregnancy risks and outcomes, patients living with HIV can now make informed choices. This chapter is written to assist physicians to help their patients fulfil their reproductive ambitions.

PREVALENCE OF HIV AND CURRENT EPIDEMIOLOGY

HIV was first identified in the early 1980s when epidemiologists noticed a clustering of cases of Kaposi's sarcoma, a rare skin tumor, in young gay men living in Los Angeles, USA[10]. HIV, the causative agent of the acquired immune deficiency syndrome (AIDS), was subsequently identified[11]. Since then, this new, emergent and, in many cases fatal, sexually transmitted infection (STI) has spread globally. The most significant health consequence is high mortality, especially among those of reproductive, and therefore working, age in the developing world[12]. Most (75–85%) cases of HIV are sexually acquired. The remainder occur as a result of drug use via injection (IDU), mother to child transmission and administration of contaminated blood products[13]. Three different patterns of sexual spread have been described. Pattern 1 is most common in the developed world where HIV has spread mostly amongst men who have sex with men (MSM). In pattern 2 countries, predominantly the developing nations, HIV has spread heterosexually. In pattern 3 countries, the numbers of cases and mode of spread are not always clear (Table 1).

DIAGNOSING HIV INFECTION

Most patients infected with HIV do not have symptoms. In the Western world, where treatment is routinely available, those at risk of HIV are encouraged to come forward for testing, as early diagnosis allows for monitoring

of immune status, and treatment interventions can be timed so that patients may derive the greatest therapeutic benefit. Despite these policies, new diagnoses are still made late in about 42% of African patients residing in the UK. This pattern is likely to be similar to that found in other countries to which native born Africans have emigrated[14,15].

A sexual history and HIV risk assessment is recommended as a routine part of the evaluation of any couple presenting for preconceptional care. Clinicians providing care should be fully aware of the risk factors for HIV, able to undertake a basic HIV risk assessment and feel comfortable explaining the advantages to individuals of knowing their HIV status.

Many Western countries offer HIV testing as part of routine antenatal care[16,17], thus allowing many women to be diagnosed in the early stages of pregnancy. In addition, it is routine in many countries to screen patients requesting treatment for infertility for HIV, again allowing some women to be identified by this route at this time. Unfortunately, neither of these settings is ideal, and in almost all so-called 'unexpected diagnoses' clear risk factors can be identified. An appropriate risk assessment at the preconceptional stage avoids this unsatisfactory situation (Table 2).

After obtaining an adequate sexual history and HIV risk assessment, patients can be encouraged to undergo a full sexual health screen, as the presence of undiagnosed and often asymptomatic STI may affect fertility, pregnancy and the new born child. In this regard, it is especially important to remember that ulcerative and non-ulcerative STI increase the risk of acquisition as well as transmission of HIV. It is for this reason that both partners should be advised to have a STI screen before pregnancy to ensure they are in the best possible sexual health.

Table 1 Risk groups for HIV infection

Risk factor
Men who have sex with men (MSM)*
Country of origin – developing countries such as Africa, Asia, India, Caribbean*
Injecting drug use*
Contaminated blood products either before blood screening or where this is not routinely undertaken*

*Or sexual contact with someone in this risk group

GENERAL REPRODUCTIVE HEALTH IN HIV POSITIVE PATIENTS

Despite all recent advances in treatment, making a diagnosis of HIV is devastating to the patient. Most newly diagnosed women are in the reproductive age range, and some will already have had children whilst others hope for them in the future[18]. Figures 1 and 2 demonstrate the increasing burden of HIV/AIDS in the female population, especially in sub-Saharan Africa.

Because many patients still believe that a diagnosis of HIV infection is at worst a death sentence and at best will mean that they can no longer expect a normal family life, the implications for the individual and her partner(s)

Table 2 Essentials of sexual history taking and HIV risk assessment

*Sexual history**
Partner 1 – timing of last sexual intercourse, with whom and from what country
Use of condoms on this occasion or during the relationship
Duration of the relationship
Partner 2 – timing of past sexual intercourse, with whom and from what country
Use of condoms on this occasion or during the relationship
Duration of the relationship

*History usually repeated to cover any partners in the preceding 6–12 months

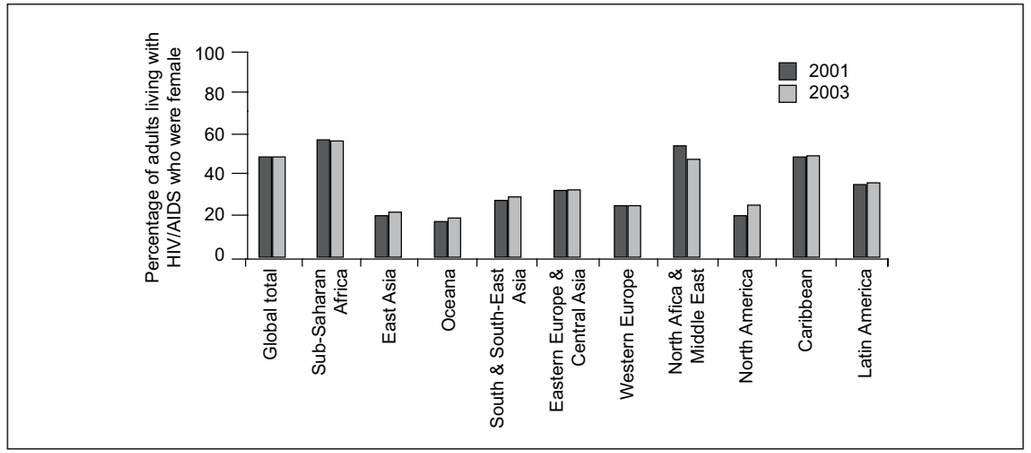

Figure 1 Estimate of percentage of adults (15–49 years) living with HIV/AIDS who were female in 2001 and 2003. (Reproduced with permission from UNAIDS/UNFPA/UNIFEM, 2004[19])

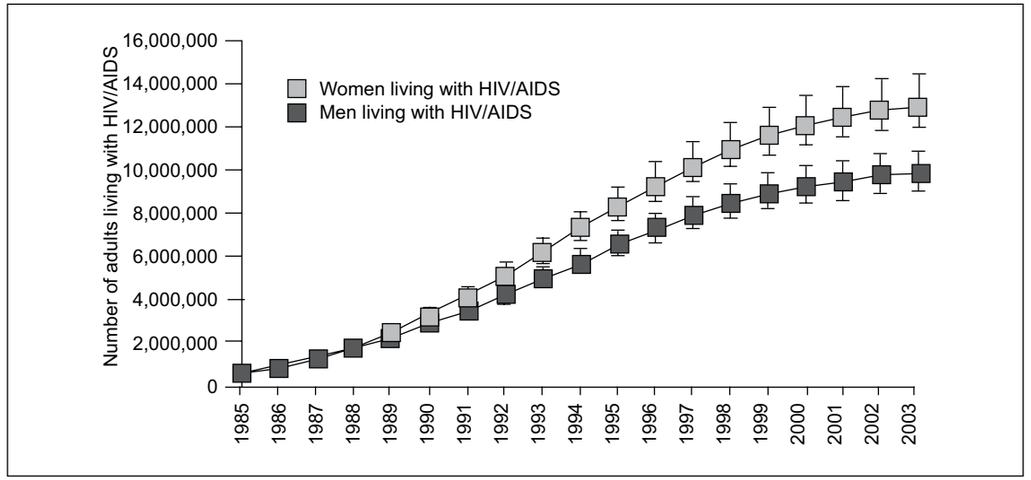

Figure 2 Estmated number of adult (15–49 years) women and men living with HIV/AIDS in sub-Saharan Africa (1985–2003). (Reproduced with permission from UNAIDS/WHO, 2004[20])

and future partners should be a routine part of early discussions. Contact tracing and the testing of current and previous sexual partners should be addressed soon after initial diagnosis. For women of reproductive age, however, such discussions should focus on prevention of onward viral transmission as well as effective contraception. For the newly diagnosed male, the status of their partner(s) and the risk of onward transmission are usually paramount. Figure 3 illustrates estimations of HIV infectivity via different routes of possible transmission. The male condom remains the most effective method of reducing

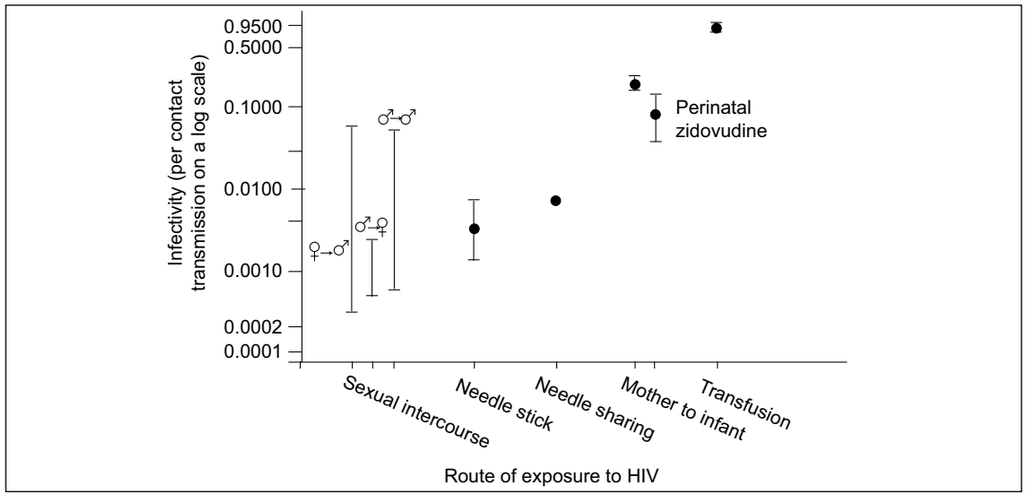

Figure 3 Probability of HIV transmission via different routes. Per contact probability of HIV transmission. The infectivity ranges for sexual contact are derived from a comprehensive review of the literature (lower and upper bounds are from modeling per contact transmission in different study populations with different modeling techniques). Each infectivity estimate for the other routes of infection originates from one representative study. The routes of infection are as follows: sexual intercourse, with ♀→♂ indicating female-to-male transmission, ♂→♀ indicating male-to-female transmission, and ♂→♂ indicating male-to-male transmission; needle stick; needle sharing; transmission from mother to infant with and without perinatal zidovudine treatment; and transfusion. (Reproduced with permission from Royce RA, Sena A, Cates W Jr, Cohen MS. Current concepts: sexual transmission of HIV. *N Engl J Med* 1997;336:1072–8[21]. Copyright 1997: Massachusetts Medical Society. All rights reserved)

virus transmission. For the prevention of an unplanned pregnancy, additional contraceptives methods may be advised.

FERTILITY AND CONTRACEPTION IN THE HIV POSITIVE FEMALE

Contraception

Information about effective contraception is critical for both pre- and post-pregnancy planning. Women should be encouraged to make informed choices regarding contraception and should be given all the information necessary to do so. Most contraceptive methods are safe and effective in HIV positive women who are not taking ART. For those who are on ART, only certain forms of contraception are regarded as effective and patients should be duly informed[22–24]. The use of condoms should be encouraged in addition to other forms of effective contraception for three separate but *related* reasons pertaining to the reduction of: (1) acquiring other STI; (2) transmission of HIV in discordant couples; and (3) possible superinfection in concordant couples. This form of dual protection is often termed 'doubling up'[1]. Table 3 provides a summary of contraceptive choices and their likely efficacy based on guidance from the UK Faculty of Sexual and Reproductive Healthcare.

When a method of contraception fails or unprotected intercourse has occurred, emergency contraception can reduce the risk of an unplanned pregnancy. Women who are not on ART may be offered the progestogen only emergency contraception – levonorgestrel 1.5 mg single dose, for use within 72 hours of sexual intercourse. An alternative is the insertion of a copper intrauterine contraceptive device (IUCD) within 5 days. For women using ART, an emergency IUCD is the preferred option, as this contraceptive method is unaffected by HIV medication. Should the woman be reluctant to use this method, then a double dose of levonorgestrel should be given as soon as possible and within 72 hours; however, use in this manner is outside the product licence.

Table 3 Summary of UK medical eligibility criteria for contraceptive use (UKMEC)

Contraception type	*HIV positive no antiretrovirals*	*HIV positive on antiretrovirals*
Combined oral contraceptive pill	1	2*
Combined contraceptive patch	1	2*
Progesterone-only pill	1	2*
Long-acting injectable progestogens	1	1
Progestogen-only subdermal implants	1	2*
Levonorgestrel intrauterine system	2	1
Copper intrauterine devices	2	2
Diaphragm and caps	3**	3**
Condoms	1	1

UKMEC category: 1, no restriction for use of the method; 2, advantages of using the method generally outweigh the theoretical or proven risks; 3, the theoretical or proven risks generally outweigh the advantages of using the method; 4, an unacceptable health risk if the contraceptive method is used.
*Some antiretrovirals cause a reduction in bioavailability by inducing liver enzymes. Additional use of condoms strongly encouraged.
**Potentially permits transmission of virus

Fertility

No hard evidence exists to show that women with HIV infection are less fertile than other women. Similarly, asymptomatic women with HIV infection do not experience disorders of menstrual function and ovulation any more frequently than HIV negative women[25,26].

Health before conception

General health should be optimized before conception, because 'early prenatal' care may well be too late for meaningful intervention, and HIV positive women are no exception. Preconception is an opportunity to address risk factors which might result in an adverse outcome for the baby or mother and to discuss possible interventions. Areas that require special attention in HIV positive women, depending on their risk factors for HIV, include diet and weight, alcohol, recreational drug consumption and psychological factors.

Healthy eating and weight management (see Chapters 22 and 30)

Whereas all patients should be encouraged to eat a healthy balanced diet and to exercise regularly, important cultural differences are present in the manner in which HIV and weight are perceived. In the African population, for

example, obesity may be perceived to be a sign of good health, and against this background it may be hard to promote a Western style healthy diet and optimum weight. This difference becomes especially important in women before and during pregnancy.

Nevertheless, issues of weight, both over and under should be specifically addressed. The UK Confidential Enquiries into Maternal and Child Health 2007 (CEMACH) report demonstrated that obese pregnant women with a body mass index of more than 30 were far more likely to die than non-obese women[27]. Under these circumstances, obese women should try to lose weight before conception wherever possible. Adverse outcomes associated with maternal obesity include increased rates of neural tube defects, preterm delivery, diabetes, cesarean sections, and hypertensive and thromboembolic disease[28–31].

Alcohol and/or recreational drug abuse

It is safest to abstain from alcohol entirely when planning pregnancy, as harm can occur early on even before a woman realises she is pregnant. The fetal alcohol syndrome and other alcohol related birth defects can be prevented if women refrain from alcohol consumption before conception. If a woman chooses not to abstain entirely from alcohol, then intake should be restricted to one unit daily[32–34].

Certain areas of the world have experienced HIV epidemics entwined with rising rates of drug abuse[35]. IDU have the highest prevalence rates for HIV, but crack cocaine users and other substance abusers demonstrate substantially elevated rates of infection as well[36]. This is probably related to risky sexual activity while on drugs. The women in this subgroup are particularly vulnerable, as they are open to physical and sexual abuse. Preconceptional counseling provides an opportunity to deal with these issues.

Immunization history

Newly diagnosed HIV positive patients are usually investigated for previous exposure to infections such as cytomegalovirus and toxoplasmosis, both of which display latency and may reactivate in late stage, untreated HIV infection[37]. Newly diagnosed patients are also usually tested for hepatitis C (HCV) infection for which IDU and MSM are the most at risk. In women who may want to become pregnant, this point in time also provides an opportunity to check rubella and hepatitis B status and vaccinate if required. In women infected with hepatitis B, neonates can be protected at birth[38–41].

Safer sex

The consistent and careful use of condoms is crucial for the reduction of HIV transmission and cannot be over emphasized. Risk of HIV transmission in women is particularly high during menstruation and in the presence of genital tract infections or lesions as mentioned above[42].

Psychological well-being

Women with HIV infection are at higher risk of depression than those without the condition. The clinical picture is complex and related in part to the premorbid personality, past history of mental health problems and risk factors for the acquisition of HIV. Depression can impact on compliance with medication and other important health interventions in a manner that is adverse to pregnancy outcome. Because of this, all HIV positive women should undergo a basic mental health assessment as part of preconceptional counseling and, if problems are identified, appropriate expert support can be sought[43].

FERTILITY AND CONTRACEPTION IN HIV POSITIVE MEN

Fertility

Few data are available on the fertility of HIV infected men, although some studies have suggested that such individuals have a reduction in sperm quantity and quality[44,45]; however, this observation is not universal. Using WHO criteria[46], provided the CD4 is greater than 200, others have demonstrated that HIV has little effect on sperm quality or production. On the other hand, men with advanced disease may have abnormal sperm production, and optimizing highly active ART (HAART) may benefit their fertility[1]. No published evidence suggests that specific ARTs affect male fertility.

Contraception

For each act of unprotected intercourse during which the man is HIV positive, the risk of transmission to a negative partner is between 1 in 500 and 1 in 1000[4,47,48]. However, the chance of transmission is cumulative with each act of unprotected intercourse. Therefore, the male condom has been of exceptional importance in the fight against HIV transmission and acquisition, accounting for a decrease in transmission risk by 80–90%[49]. Considering this circumstance alone and irrespective of any desire to avoid an unwanted pregnancy, the use of the condom should be encouraged to prevent the spread of HIV, superinfection (re-infection with a second strain of HIV after the first infection has been established in concordant couples) and co-infection with other STI.

This having been said, education in the proper use of condoms with water-based lubricants not containing nonoxynol-9, rather than oil-based lubricants is of paramount importance, as oil-based lubricants damage latex condoms and increase breakage rates. In contrast, the thickness of condoms does not appear to add any additional benefit with regards to protection[1,50].

PREGNANCY IN HIV POSITIVE WOMEN

Pregnancy is not harmful to women with HIV infection and women should be informed of and reassured by this fact[51–54]. The effect of HIV on pregnancy outcome is discussed below.

Optimal timing of pregnancy

This issue is related to two distinct points, the first being the timing of pregnancy in relation to female fertility and the second being timing in relation to HIV disease status. Patients with HIV infection are offered routine medical follow-up every 3–6 months in those countries where HIV is treated as a chronic and ongoing infection. Unfortunately, such care is not available worldwide. At these visits, the CD4 count (white cells targeted by HIV) and viral load (HIV viral load levels in plasma) are measured and general health reassessed. This information is then used to advise on the timing of ART. Broad indications for starting ART include:

- Symptomatic HIV infection regardless of CD4 count and HIV viral load
- CD4 counts below 350/mm^3 (normal range 500–1000/mm^3)
- Patients with a high viral load (i.e. >30,000 copies/ml)[55].

UK guidelines recommend starting ART in established HIV infection following two consecutive CD4 samples below 350/mm^3 without any obvious explanation for the fall[56]. The guidelines from the International AIDS Society, USA (IAS-USA) are along similar lines[57] as are WHO guidelines[55].

Antiretroviral choice

A wide range of drugs are available for the treatment of HIV[58]. However, the selection of the appropriate agent is an increasingly complex science, and all HIV positive patients, especially those requiring treatment, should be managed by HIV specialists familiar with the complexities and side-effects of ART. If a woman needs to start treatment and there is a possibility of pregnancy in the future, this fact by itself will impact on the choice of drugs. The exact choice of medications is influenced by a number of issues including:

1. The CD4 count at initiation of therapy;
2. The baseline resistance profile, if resources are available to perform this test which is designed to detect the presence of virus which has developed resistance to available drug treatment;
3. The availability and cost of drugs especially in resource-limited settings.

Authoritative sources of further information include the British HIV Association guideline[59], Perinatal HIV Guidelines Working group[60] and WHO Recommendations 2010[61].

Antiretroviral therapy for maternal health

Antiretroviral therapy should be started for the benefit of maternal health if advised by a HIV specialist. If this decision comes at a time when the woman is in the first trimester of pregnancy and yet to start HAART with a CD4 of more than 200 cells/mm^3, then the ART may be delayed until the end of the first trimester[62].

HAART for prevention of mother to child transmission

For women who do not require ART for their own well-being, it should be used to prevent vertical transmission which would be between 15 and 40% without ART[3,63–65] and less than 2% with appropriate intervention. Because vertical transmission can occur at various stages in the peripartum period including delivery and during breastfeeding, these are the main areas where interventions are aimed. When ART is commenced in pregnancy solely to prevent vertical transmission it is termed short term antiretroviral therapy (START). When used in this context ART is stopped in the postpartum period. The optimal timing for initiating START should be before fetal viability, at around 24 weeks' gestation, with the aim of achieving an undetectable viral load (quantum of virus in plasma) before delivery, as this reduces transmission risk to 2%[60]. Women who have persistently low viral loads (<10,000 copies/ml) and require ART only for prevention of mother to child transmission (PMTCT) may opt for zidovudine (ZVD) monotherapy starting at a similar gestational age as described above. An elective cesarean section at 39 weeks' gestation is advocated in these situations. Women on ZDV have a lower incidence of preterm deliveries (PTD) compared to women on multiple antiretrovirals. Although prematurity has been associated with the use of an increasing number of antiretrovirals[58], the huge benefits provided by these agents far outweigh the risk and they should not be withheld.

GETTING PREGNANT

Concordant (both HIV positive) couples

In concordant couples, a theoretical risk of HIV 'superinfection', i.e. transmission of different strains and/or types of HIV with different resistance profiles, is present if condoms are not used[1]. Patients should be made aware of this, counseled against unprotected intercourse and sperm washing advised when attempting to conceive[1,26]. In situations where

this is neither affordable nor available and the couple decide to attempt pregnancy through unprotected intercourse it may be pragmatic to focus advice on the timing of unprotected intercourse during the fertile period. At all other times condoms should be used.

Discordant couples

HIV positive female and HIV negative male

The couple should be advised regarding the use of timed self insemination around the ovulation period. Intercourse should ideally be protected with ejaculation into a non-spermicidal condom. Self insemination of the semen can then be performed with a needleless syringe which is then deposited in the vagina close to the cervix. Turkey basters can be used but clinics often provide women with 10/20 ml syringes. This is well documented and practiced.

HIV positive male and HIV negative female

The main risk in this circumstance is that the woman becomes infected whilst trying to conceive. A number of options can minimize this risk.

Insemination using donor sperm Donor sperm totally excludes the risk of infecting the partner. All sperm donors are screened for blood borne viruses. The drawback of this methodology, however, is that the child conceived will have no genetic relationship to the 'father'.

Sperm washing This is an effective and safe, risk reduction option if undertaken properly as shown by data from Italy and the UK[6]. It is important to inform the couple that this process is not a risk free option, but rather represents a risk reduction option. What is the risk that the sample might be HIV positive after washing? The risk of the washed sample having detectable HIV is 5–6%[66–68]. After washing, 5–6% of semen samples are HIV polymerase chain reaction (PCR) positive using the ultrasensitive assay. This assay detects more than 25 HIV copies/ml. Such samples are obviously discarded. Thus, HIV testing of the washed sample is recommended. The process of sperm washing involves separation of the spermatozoa from the infected seminal fluid and non-sperm cells. The female partner is then inseminated with the washed sperm. Documented success rates of ongoing pregnancies from various centers range from 12.5 to 27.7%[4,68,69].

Use of ART UK and American guidelines discourage unprotected sexual intercourse regardless of the duration of HIV infection and plasma viral load[1,70]. This includes couples where the infected male partner is on ART and has an undetectable viral load, due to the fact that the viral load in semen correlates poorly with that in serum[3,71,72]. Accordingly, men with undetectable plasma viral loads can still transmit HIV in semen where the testes act as a 'sanctuary site'[73].

Adoption This is a final option, although clearly the child will not have a genetic relationship to either parent.

PREGNANCY PROBLEMS IN HIV POSITIVE WOMEN

First trimester

Early referral to an obstetrician is advised, preferably as soon as a pregnancy is confirmed.

Nausea and vomiting

These symptoms are common in early pregnancy and are usually resolved by the second trimester. The occurrence of nausea and vomiting can affect women taking ART; however,

patients should be advised to adjust their pill timing if necessary.

In HIV positive women on ART, a diagnosis of hyperemesis should only be made once all organic causes have been ruled out, especially lactic acidosis, hepatitis and pancreatitis, all of which may be complications of ART. Antiemetics that are safe in pregnancy may be used. There are no known interactions between antiemetics and antiretrovirals.

Miscarriage rate

There is no evidence of an increased risk of miscarriage in HIV positive patients[63,74,75], although the risk of preterm delivery may be increased with increasing numbers of ART. In certain circumstances, as mentioned above, it may be reasonable to use a single ART. However, even with the possible risks of multiple ART use, the benefits of preventing mother to child transmission outweigh the small risk of miscarriage.

Fetal abnormality

HIV is not associated with an increased rate of fetal abnormality. To date, two ART are best avoided in pregnancy: didanosine increases the fetal abnormality rate above the expected background risk, and efavirenz has been associated with congenital malformation in macaques. This drug is contraindicated in pregnancy or in women who may wish to conceive.

Preterm delivery

The risk of preterm delivery is increased with HAART[59]. However, the HIV positive woman presenting with threatened preterm delivery should be managed in the same manner as the HIV negative woman. If preterm rupture of membranes occurs after 34 weeks, delivery should be expedited after an infection screen, paying particular attention to genital infections. Antibiotic coverage is advised.

If there is preterm rupture of membranes at less than 34 weeks, the clinician should balance the risks of fetal prematurity against prolonging the pregnancy. The maternal viral load, HAART and any maternal co-morbidities need to be considered and a multidisciplinary approach is advisable.

Postpartum

Breastfeeding and the mode of delivery can be discussed during preconceptional counseling and in early pregnancy.

Breastfeeding

Because breastfeeding is associated with a two-fold increase in the rate of HIV transmission, it is not advised in resource rich countries[58]. Women should be made aware of this possibility at a stage early enough to discuss any concerns. Pharmacological suppression of lactation can be considered postdelivery if necessary.

Mode of delivery

Elective cesarean section reduces MTCT[58,65]. The final decision on mode of delivery requires a balancing of the risks of maternal complications with benefits. Factors to be considered are the maternal viral load, past obstetric history and use of HAART. Evidence is emerging that viral control and other interventions in the perinatal period may sufficiently reduce risk to enable clinicians to allow vaginal deliveries in some settings where there is optimal control[76,77].

Fetal blood test

In the developed world the neonate will be given ART from birth usually for a period of

1 month[55]. The gold standard test for HIV infection in infancy is an HIV DNA PCR on peripheral blood lymphocytes. The infant is tested at 1 day of life, and 6 and 12 weeks of age. If all tests are negative and the infant is not breastfed, the child is deemed HIV negative. Antibody tests for HIV are only reliable at 18 months because of detectable maternal antibody prior to this age.

CONCLUSION

In the late 1980s and early 1990s HIV was largely untreatable and women were strongly advised not to have children. The development of ART has transformed approaches to care. Patients with HIV can look forward to a much longer and healthier life. They can also consider childbearing with a less than 2% risk of transmission to the child if good preconceptional and antenatal care is provided. The future goal of successful vaccination to prevent primary infection remains elusive but not impossible.

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16
Infectious diseases in preconceptional care

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Consensus is developing that acting prior to pregnancy for a number of disease states could improve reproductive outcomes; infectious diseases are no exception. The means by which infections have an impact on reproductive outcomes are almost as varied as the diseases themselves. For example, infections in the preconceptional period can affect both male and female fertility factors, leading to decreased fecundity or actual infertility. They can also affect early pregnancy in an 'all or nothing' fashion if they cause spontaneous abortion. Congenital infection of varying degrees of severity also can occur, in many cases with minimal maternal illness. Infections can affect the mother, leading to either maternal or obstetric complications with eventual preterm delivery or maternal death followed by death of the fetus.

Infections may be acquired either prior to or during pregnancy; both can affect neonatal outcomes. An additional possibility is that the fetus may be free of disease owing to the barrier imposed by the placenta, but acquire infection at birth through vertical transmission. Infections can affect the vulnerable infant especially in the early neonatal period due to an immature immune system. Preconceptional interventions to reduce the impact of infections include preventing infection through immunization, safer sex initiatives and needle exchange programs; reducing the quantity and location of an infectious agent, such as prevention of diarrheal disease through improved sanitation; and, finally, reducing the effects of an infection on the host, especially in chronic infections and/or repeated episodes of acute infections leading to immunocompromise in the host.

Considering that any infection is the result of interactions between the host, the agent and the environment, preconceptional interventions can occur in any of these areas to reduce the impact of an infectious disease on reproductive outcomes. Initiatives such as changing the environment through interventions aimed at reducing poverty or promotion of breastfeeding can have a positive impact on infectious disease outcomes. Finally, infectious diseases are diverse in their impacts and in the manner in which interventions can occur, all types of infectious agents with preconceptional implications have been identified including viruses, bacteria and parasites; however, prion-caused infectious diseases have yet to be investigated fully.

METHODS

Burden of disease was used to prioritize those diseases selected for review. Diseases were divided into those affecting women of reproductive age, pregnant women and infants. For women of reproductive age, infectious conditions including HIV/AIDS, tuberculosis and maternal sepsis are significant contributors[1]. In Africa, in particular, HIV/AIDS, TB and malaria along with 'other infectious and parasitic diseases' make up about one-third

of the disease burden[1]. Meanwhile, for childhood deaths, those occurring in the neonatal period (days 0–28 of life) comprise 37% of all deaths for children aged 0–5 years; 25% of these neonatal deaths are a result of neonatal infections, 3.4% neonatal tetanus and 2.6% diarrheal disease. Other causes of neonatal deaths are those due to prematurity and low birth weight (31%) and congenital anomalies (6.7%) which can have an infectious etiology component[1]. Finally, many of the remaining deaths before age 5 (postneonatal) are communicable including acute respiratory infection (17%), diarrheal disease (16%), malaria (7%), measles (4%), HIV/AIDS (2%) and other infections and parasitic diseases (9%). Together, these infectious diseases account for about 55% of deaths in 0–5 year olds[1]. Under these circumstances, the prime focus of this chapter includes HIV/AIDS (see also Chapter 15), tuberculosis (see also Chapter 14), malaria, neonatal acute respiratory infection, neonatal diarrheal disease, measles, neonatal tetanus, neonatal infections (sepsis and meningitis), infection-related preterm birth, low birth weight and congenital anomalies/infections. Finally, Chlamydia, gonorrhea and hepatitis (B and C) receive specific attention in the category of 'other infectious disease'. Each is considered separately.

HIV/AIDS

HIV/AIDS is the leading cause of infectious complications and deaths worldwide. In 2008, 33.4 million people were living with HIV, including 2.1 million children (most secondary to maternal–child transmission), with 480,000 incident cases in children. Also in 2008, there were 2 million deaths, with 280,000 deaths occurring in children[2]. HIV/AIDS is a significant causal factor in maternal and infant deaths[2,3]. In well resourced countries, however, neither consequence needs to be frequent[4], as effective antiretroviral treatment is available for some women and for all during pregnancy[5]. There are specific recommendations to screen preconceptionally those with risk factors and, in countries where many incident cases have no risk factors, to offer screening to those with no risk factors[6,7].

Screening may be initiated voluntarily or via provider initiated testing with an opt-out approach being recommended (*a patient be must given the opportunity to specifically request that an HIV test is not performed*)[7,8]. Knowing a potential mother's HIV status in the preconceptional period is important since treatment ideally should begin early in pregnancy. (Current WHO recommendations are to begin antiretroviral therapy at around 14 weeks (in the second trimester), as transplacental transmission to the fetus can occur this early (recommended for women who are HIV positive and early in the disease process – normal CD4 count and no HIV associated illness)[5].) Furthermore, for women who are symptomatic or with low CD4 counts, antiretroviral therapy is recommended throughout pregnancy[5].

Other components of preconceptional care include primary prevention of the disease, such as public health campaigns to decrease transmission including condom use, male circumcision, needle exchange programs or any combination of these initiatives[9,10]. For couples where one partner is HIV positive, a reproductive life plan should be developed[11]. One recommended question for this is, 'What are your thoughts about having children now that you are HIV-infected?'[11] Information provided to the patient and her partner (if available) should include the fact that pregnancy does not alter the course of HIV infection for an infected woman and the distinct and clear risk of maternal–child transmission; information on the availability of antiretroviral therapy during pregnancy and at the time of delivery; and the possible recommendation for cesarean delivery to prevent transmission[11]. For couples wishing to defer childbearing, appropriate contraception must be offered.

Barrier contraception should be recommended for all couples – even those in which both are HIV infected, as transmission of different HIV types/subtypes is possible[11]. An antiretroviral containing microbiocide vaginal gel may prevent the primary acquisition of HIV, a recent advance which should be of benefit for discordant couples[12,13].

For those wishing to pursue pregnancy, on the other hand, prevention of transmission at conception through sperm washing (male infected and female uninfected) or donor insemination (male uninfected and female infected) is recommended[14]. Timing of conception is best done in the setting of a maximally suppressed[15] or undetectable[11] viral load. Medications taken by HIV infected women considering pregnancy should be reviewed and altered as required[11]. For example, efavirenz is contraindicated in the first trimester owing to the risk of neural tube defects[11,15].

Other issues to be discussed include the importance of prenatal care, that pregnancy does not appear to alter the course of the HIV disease[11], and the increased risk of maternal death (much of the maternal mortality due to HIV/AIDS is considered to be as a result of obstetric causes[16,17]). Of interest, fertility may be impaired in HIV infected women, due to tubal factor[14,18], such that advanced reproductive therapy may be needed, and is available in certain settings[14]. Other recommendations for preconceptional care include being in good health, folic acid supplementation as recommended in other sections of this text as well as other general considerations for preconceptional health; this dictum is applicable to all conditions considered in this chapter[15].

TUBERCULOSIS

A total of 700,000 women die each year globally as a result of tuberculosis (TB)[19]. In areas with a high prevalence of TB, women of reproductive age bear the highest burden of suffering[19]. If the woman does not have TB induced infertility and if she is able to become pregnant, the consequences of TB in pregnancy include fetal death, low birth weight, growth restriction, premature birth and, rarely, congenital tuberculosis[19,20]. These outcomes are more likely in women co-infected with HIV[19].

The current worldwide strategy for TB prevention aims to detect TB and provide treatment using DOTS (directly observed therapy, short course)[21]. Other important components of the 'DOTS' strategy include political/community commitment to addressing TB; quality diagnostic procedures (positive sputum smears being the most broadly applied diagnostic technique, with other forms also being detected, i.e. extrapulmonary, smear negative and resistant TB); widespread availability of medications; and assessment of program outcomes[21]. In some developed countries, strategies include the detection of TB in the latent form to prevent progression to active TB[22]. Finally, the Bacille Calmette-Guérin (BCG) vaccine is also available and used, in many countries with a high burden of TB, soon after birth to prevent early childhood TB; this is most effective in infants who are HIV negative[23]. That HIV positive infants receiving the BCG vaccine can develop disseminated BCG has led to recommendations that the vaccine be avoided in HIV positive children[24]. This poses a challenge in areas with high rates of HIV and poor availability of the special diagnostic tests needed to diagnose HIV in newborns[24,25]. The vaccine is not effective for the prevention of adult pulmonary disease[24] and is also contraindicated in pregnancy[23]. Currently, WHO recommends the vaccine for adults exposed to multidrug resistant TB[23].

Diagnosis and treatment of TB prior to pregnancy would have the advantage of potentially avoiding risks of treatment with drugs which could be harmful to the fetus such as streptomycin, fluoroquinolones, or those with few safety data in pregnancy such as pyrazinamide, although most first-line drugs are considered

safe in pregnancy[20]. Finally, if latent tuberculosis infection (LTBI) is to be the target of treatment, as treatment is often withheld during pregnancy based on reasonable concerns of a higher risk of isoniazid induced hepatotoxicity, it may be reasonable to treat in the preconceptional period[6].

MALARIA

Malaria is very common globally, with about 50 million pregnancies occurring annually in malaria endemic areas[26]. Malaria is a mosquito-borne infectious disease caused by a eukaryotic protist of the genus *Plasmodium*. Five species of the *Plasmodium* parasite infect humans; the most serious forms of the disease are caused by *Plasmodium falciparum*. Malaria caused by *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae* results in milder disease in humans and are not generally fatal.

Malaria is naturally transmitted by the bite of a female *Anopheles* mosquito. When a mosquito bites an infected person, a small amount of blood is taken, which contains malaria parasites. These develop within the mosquito, and about 1 week later, when the mosquito takes its next blood meal, the parasites are injected with the mosquito's saliva into the person being bitten. After a period of between 2 weeks and several months (occasionally years) spent in the liver, the malaria parasites start to multiply within red blood cells, causing symptoms that include fever and headache. In severe cases the disease worsens leading to hallucinations, coma and death.

Direct complications of malarial infection in pregnancy include miscarriage, growth restriction, low birth weight, premature delivery and maternal anemia[27]. Malarial deaths (2.7 million per year) are concentrated in sub-Saharan Africa where children under 5 account for 75% of global deaths[27]. Pregnancy poses some increased risk of infection, as there is some evidence of pregnancy representing increased attractiveness to the mosquito carrier[28], as well as the pregnant woman being infected by the parasite[27].

Women at highest risk of infection are those with a first pregnancy, in the second trimester, HIV infected or those with no immunity to the infection[27]. While many pregnant women are asymptomatic, there is also a higher risk in pregnancy of anemia, cerebral edema, pulmonary edema and hypoglycemia[29]. Congenital malaria is defined as infection of the fetus or newborn. Risks of congenital malaria depend on the immune status of the mother – risk is highest in those with low levels of immunity[27]. Immunity waxes and wanes in pregnancy depending on antibody levels which may in turn be mediated by continued exposure to the parasite (for example, women from endemic areas moving to non-endemic areas may be at higher risk due to reduced exposure to the parasite)[27].

Acquisition by the fetus occurs through transplacental spread in most cases, although up to 40–50% of newborn cases involve either a different genotype or no evidence of placental infection in some studies[27]. *Plasmodium falciparum* is the protozoa which poses the greatest risk for the mother and fetus, and is the only species involved in placental infection[27]. Chloroquine administered on a weekly basis has been used as a preventive mechanism (with evidence that it prevents anemia and low birth weight) and is especially effective if given early in pregnancy (first and second trimester)[27]. However, resistance and compliance with the regimen are problematic, and its use is limited[27]. Intermittent preventive treatment in pregnancy (IPTp) has been recommended more recently for areas of high transmission – two courses of treatment 1 month apart in the second trimester with sulfadoxine-pyrimethamine[30], with evidence that this treatment improves hemoglobin levels and birth weight[27]. Insecticide-treated bed nets are another preventive strategy along with recommendations for IPTp[30].

Finally, effective case management is recommended in areas of low and high transmission[30]. In women with co-existing HIV infection, the risks of malaria infection for the mother and fetus are more severe in part probably as a result of immune dysfunction[27,29]. More frequent IPTp may be recommended in these women as well as preventive measures to avoid exposure to the mosquito[27]. Trimethoprim-sulfa (cotrimoxazole), which is used for prevention/treatment of opportunistic infections in HIV, is efficacious against malaria and there is some evidence that the protease inhibitors may also inhibit malaria parasites[27].

For pregnant travelers who are non-immune (or usually reside in non-endemic areas), travel to endemic areas should be avoided. If travel is necessary, prevention strategies (bed nets and *N,N*-diethyl-*meta*-toluamide (DEET) containing insecticides which are safe in pregnancy) and chemoprophylaxis are recommended. In these circumstances, chloroquine only should be administered in areas were resistance is not documented or combination treatment with various regimens depending on resistance and the presence/absence of *P. falciparum* in the area (see the CDC's 'Yellow Book' for the most current recommendations http://wwwnc.cdc.gov/travel/content/yellowbook/home-2010.aspx)[31].

Prophylaxis with IPTp prevents complications in pregnancy; however, this has not been recommended in the first trimester, and there are no recommendations for prophylaxis in the preconceptional period other than for those traveling from non-endemic to endemic areas[30].

ACUTE RESPIRATORY INFECTIONS

Acute respiratory conditions including pneumonia and pertussis, led to an estimated 1.8 million deaths of children 0–5 years old in 2008[32]. Pneumonia is the leading cause of death from acute respiratory conditions, accounting for 1.5 million of the 1.8 million fatalities (with 386,000 occurring in neonates)[32]. Most recommendations to deal with this disease target children directly, and include early recognition and treatment, promotion of exclusive breastfeeding (itself an interconception intervention[33]) and vaccination against pneumococcal pneumonia, measles, *Haemophilus influenza* type b (Hib) and pertussis[34]. Vaccinations are promoted since pneumonia can be caused either directly by the organism targeted by the vaccine (the pneumococcal or Hib vaccines) or by a complication of vaccine preventable conditions such pertussis, measles (the latter is considered in a separate section) and influenza (although this particular vaccine is not a recommendation of the UNICEF strategy for pneumonia). Accordingly, vaccination of women for these conditions in the preconceptional period might prevent some of the deaths arising from the conditions through passive immunization or decreasing household transmission, especially to neonates.

In one study, administration of pneumococcal vaccine in pregnancy increased maternal, breast milk and infant antibody levels[35]. However, another study demonstrated only modest increases in antibody levels in mothers when the vaccine was administered in the preconceptional period and no significant increases in neonatal antibody levels[36]. This same study did provide data, however, to suggest that the *Haemophilus influenza* type b vaccine, when administered to women before pregnancy, led to protective antibody levels at birth, and in the immediate postnatal period to higher antibody levels in the neonate[36]. Unfortunately, these studies[35,36] are limited in that they did not examine whether vaccination in pregnancy or in the preconceptional period prevented subsequent disease in infants.

Pertussis is a condition which leads to chronic cough. Between 300,000 and 600,000 cases are estimated to occur in the US each year (in adults); worldwide in 2003 there were 17.6 million recorded cases[37,38]. As the number

of recorded cases invariably underestimates the total number because of underreporting, it is likely that the prevalence of this condition is even higher than the numbers provided suggest. More than 90% of the annually estimated 279,000 deaths occur in developing countries[38]. Because infants under 12 months are especially susceptible, a strategy of early immunization and passive immunization of the newborn has been proposed[39]. Currently CDC recommends giving the vaccine to the mother in the immediate postpartum period to avoid early onset disease in the newborn[40]. As the vaccine is not a live vaccine, it can be administered during pregnancy; this practice is often avoided because of limited safety data. A strategy of giving the vaccine during the preconceptional period has the advantage of avoiding these concerns and ensuring that the mother has fully developed an immune response before delivery[41].

Influenza is estimated to cause 250,000–500,000 deaths a year worldwide in its seasonal form[42]. In the US, a pandemic form H1N1 virus was estimated to have affected 61 million individuals and caused 12,000 deaths between April 2009 and April 2010[43]. H1N1 was in a pandemic form during its worldwide circulation in 2009 and 2010; it was recently declared to be postpandemic by WHO, although is it predicted to remain in circulation as one of the seasonal forms of the virus[44]. Vaccination against the influenza virus, including H1N1, is an effective prevention strategy; however, revaccination is required on an annual basis due to changes in the virus each year[45]. In the US, annual flu vaccination is recommended for all individuals over 6 months of age[45]. The inactivated form (not the live virus form) is recommended for women during pregnancy as it is documented to be safe[45]. Vaccination prior to pregnancy with either form of the vaccine is recommended for women who may be pregnant during the flu season[46]. These recommendations are put forward to prevent maternal complications during pregnancy and newborn illness, both of which can be severe[45].

Diphtheria is another preventable (by vaccination) acute respiratory infection[46]. It is distinct from other respiratory conditions in that its classic manifestations occur in the upper airway (pharynx, nasal mucosa and palate) in the formation of a gray membrane[46], a rare but potentially fatal circumstance in which death occurs via airway obstruction[46]. Routine vaccination in childhood prevents this condition; however, it is unknown whether vaccination of women of childbearing age would result in lower rates of neonatal disease before routine vaccination of children can be accomplished. Diphtheria is part of the Tdap vaccine recommended for adults as a preconceptional strategy to prevent pertussis in the US, and is part of the Td vaccine recommended as a booster dose in adults to maintain lifelong immunity[47].

DIARRHEAL DISEASE

It is estimated that 1.5 million deaths occur in children from some form of diarrhea each year; many of these are concentrated in South Asia and Africa[48]. Of the many recommended prevention strategies, one intervention, that is, face-to-face counseling to promote exclusive breastfeeding, is part of the worldwide strategy to prevent the disease[48]. Breastfeeding is particularly recommended because it is associated with a 6-fold decreased risk of death from diarrheal disease in the first months of life[49]. Also included in the global strategy are the promotion of the administration of measles (see section below) and rotavirus vaccines in children. Because the rotavirus vaccine currently has a maximum age limit for administration of 32 months, its use as a provider of passive immunity in mothers preconceptionally has not been tested. Although not part of the global diarrheal disease strategy, a cholera vaccine exists for endemic areas, and pregnant women have been prioritized for vaccination[47].

Childhood undernutrition is another contributor to mortality in diarrheal disease, as there is growing evidence that at least some underweight may have its origin in preterm birth and growth restriction (see below). Under these circumstances, preconceptional interventions may assist indirectly in preventing diarrheal disease[50]. Interestingly, diarrhea in women of childbearing age has been shown in one study to be a risk factor for neural tube defects, most likely due to decreased absorption of folic acid[51]. Here also, prevention efforts that secondarily benefit adults may have preconceptional health benefits.

MEASLES

Measles is a common disease worldwide and is most easily recognized by a maculopapular rash preceded by a high fever, coryza, cough and conjunctivitis[52]. Complications include pneumonia and diarrhea, both of which are implicated in mortality associated with this condition. Those most vulnerable live in developing countries and are young children with undernutrition, vitamin A deficiency and immune dysfunction such as HIV[52]. Other complications include otitis media and postmeasles encephalitis[52]. Onset in pregnancy has been associated with miscarriage, low birth weight and preterm birth[52].

Measles containing vaccines (MCVs) most commonly used are either MMR (mumps, measles, rubella) or MMRV (mumps, measles, rubella, varicella); all are live virus vaccines which should be avoided in pregnancy[53]. Use of these combined vaccines is recommended in countries which can achieve high levels (>80%) of population vaccine coverage[47]. Measles containing vaccines are part of childhood recommended vaccine programs, and long-term immunity has been demonstrated[53]. Adults traveling to areas with a measles outbreak and health care workers have been prioritized to obtain booster doses[52]. The contribution of a similar program for women preconceptionally has not been assessed as a strategy to prevent pregnancy complications or for protection of the newborn (although the latter is possible given that IgG antibody, which crosses the placenta, is produced as a result of vaccination; however, in titers that are lower than natural infection[54]). It should be noted, however, that adults who cannot demonstrate evidence of previous vaccination are recommended to receive a two dose series[52].

TETANUS

Tetanus is an infection of wounds caused by the inoculation with *Clostridium tetani* spores which are ubiquitous in the soil[55]. When such wounds are oxygen poor, this leads to the production of a neurotoxin and tetanus symptoms: lockjaw (trismus) and muscle rigidity, including rigidity of the musculature required for respiratory function[55]. Neonatal tetanus is caused by acquisition of the spores through the umbilical stump; when disease develops, the fatality rate is very high[55,56]. Such cases are associated with insufficient or total absence of cleanliness at delivery and are more likely to occur in areas with low coverage of tetanus toxoid[55,56].

The 59,000 infants estimated to have died worldwide of neonatal tetanus in the last reported year represent a substantial reduction (92%) from the late 1980s[56]. Major contributors to this decline have been efforts to improve the cleanliness of instruments to cut the umbilical cord at birth and improved tetanus toxoid coverage[57]. A recent meta-analysis estimated that a strategy of two injections of tetanus toxoid in reproductive age women, including pregnant women, would reduce neonatal tetanus mortality by 94%[58]. Protection from tetanus is best achieved through immunization in childhood followed by periodic booster dosing in adolescence and adulthood[47]. Areas with high rates of maternal/neonatal

tetanus are recommended to undertake special efforts to ensure coverage of women of childbearing age and who are pregnant[57].

NEONATAL INFECTIONS

Neonatal infections, aside from those mentioned above, include neonatal sepsis and neonatal meningitis. Many of the efforts aimed at reducing the neonatal sepsis disease burden are postnatal interventions and early detection and treatment[59]. In certain settings, this incorporates home-based treatment[60]. No specific preconceptional interventions for this condition are available, but some diseases causing sepsis might benefit from preconceptional healthcare.

One cause of neonatal sepsis, group B streptococcus infection, is best prevented with specific treatment in pregnancy and not in the preconceptional period[2]. Higher risk of mortality and morbidity from sepsis is present when births are preterm, following preterm rupture of membranes, maternal chorioamnionitis and low birth weight[61]. Preconceptional interventions which prevent these conditions would therefore have indirect effects to prevent neonatal sepsis.

Most cases of neonatal meningitis are caused by similar organisms to those that cause neonatal sepsis; these include Gram negative bacteria such as *Escherichia coli* and *Klebsiella* sp, and group B streptococcus (with Gram negative bacteria being a more common etiology in developing countries)[63]. In the US, the rate of bacterial meningitis is 0.3 per 1000 live births and 0.02–0.5 per 1000 herpes simplex meningitis (see Congenital infections section below)[62].

Listeria monocytogenes is the third most common pathogen identified in cases of neonatal meningitis in the US. Current preconception recommendations include the avoidance of foods prone to develop listeria, including unpasteurized dairy products and to cook certain foods to steaming levels[6]. Its inclusion as a preconception recommendation is due to its association with early pregnancy loss and severe maternal illness early in pregnancy based primarily on expert opinion[6]. This pathogen is also association with preterm labor, chorioamnionitis, stillbirth and neonatal sepsis of early onset[63].

Neisseria meningitides (meningococcus) causes most meningitis, with infants aged 3–12 months being the most vulnerable in endemic areas[64]. The greatest number of cases occur as epidemic or endemic forms in sub-Saharan Africa[64]. Passive immunization of neonates occurs from maternal antibodies[64]. Furthermore, IgA in the breast milk of vaccinated mothers may be protective[65]. As a consequence, some authors suggest that maternal immunization be 'considered'[65], although it is not known whether a strategy of preconceptional immunization would be beneficial.

PRETERM BIRTH/LOW BIRTH WEIGHT

This section discusses infection-related preterm birth/low birth weight. As much low birth weight is related to preterm delivery, discussion does not consider term low birth weight due to growth restriction related to maternal smoking, multiple births, chronic medical conditions or hypertensive disorders, all of which are beyond the scope of this chapter.

A small number of those with term low birth weight that might be infection related are owing to congenital infection and are considered below. It has long been recognized that a proportion of preterm births are infection related, as they are preceded by clinical chorioamnionitis, occurring in association with either preterm labor or preterm premature rupture of membranes[66]. Further reinforcing this concept are studies which have shown that a significant proportion of these births are as a result of subclinical infection[67]. Finally, a

number of observational studies show associations between preterm births and a variety of infectious conditions such as asymptomatic bacteriuria, bacterial vaginosis, periorodontal disease and chlamydial infection (see below).

Asymptomatic bacteriuria in pregnancy is associated with significant maternal morbidity, as it leads to acute pyelonephritis. Based on a number of randomized trials, screening and treatment of this condition has been recommended as a means of preventing both maternal illness in pregnancy and low birth weight[68]. However, to date, no evidence supports screening in the pre-pregnancy period, and it is not currently recommended[2]. Similarly, following observational studies which demonstrated associations, randomized trials have been conducted of treatment in pregnancy for infections, such as bacterial vaginosis, trichomoniasis and periodontal disease. Results of these trials have been disappointing, yielding no improvement of preterm birth rates in most cases when comparing treated versus untreated women[68]. This circumstance then sparked debate about the sufficiency of the treatments, choice of antibiotics and also led to hypotheses that treatment undertaken in pregnancy may be 'too late', as the etiology of the preterm birth is postulated to be as a result of chronic inflammation caused by these diseases[69,70]. In order to address this potential deficiency, a limited number of investigations of treatment prior to pregnancy, in both observational studies and randomized trials[69,71,72], were initiated. To date, these efforts have not yielded results that have led to recommendations to screen and treat these conditions in the preconceptional period[72]. It should be noted, however, that detection and treatment may be made on other grounds[73]. Given the body of evidence showing the link between infection and preterm birth, and the significant burden of disease imposed by this association, a need clearly exists to test with properly conducted randomized trials the hypothesis that screening and treating conditions associated with preterm birth in the preconceptional period is of benefit.

Another etiology of preterm birth and second trimester loss is cervical incompetence which, in certain instances, is less directly a complication of infectious disease. This condition may result from prior surgery on the cervix such as conization or loop electrosurgical excision procedure (LEEP)[68] performed to treat cervical dysplasia which itself is due to infection with the human papilloma virus (HPV). Currently two vaccines[47] protect against the HPV types which cause most cervical cancers. To the extent that the vaccine can protect against the development of cervical dysplasia and lead to fewer cervical ablative procedures, the HPV vaccine has been considered a preconceptional intervention[41].

CONGENITAL INFECTIONS

Congenital infections can cause disease in both the mother and, by definition, in the fetus through transplacental transmission if they occur in pregnancy. These make up the so called TORCH (toxoplasmosis; others including syphilis and parvovirus; rubella; cytomegalovirus (CMV); and herpes virus infections (herpes simplex and varicella)) infections. All but toxoplasmosis and syphilis are viral infections. The primary area of concern for perinatal medicine is their transplacental spread and subsequent disease for the fetus. This type of spread also occurs with other infections mentioned above, such as HIV and influenza, but in these instances it is quite rare and not the primary consideration. Although herpes simplex is of more concern due to vertical transmission at birth, congenital infection also occurs. Finally, in a number of cases maternal disease is mild, asymptomatic or with nonspecific symptoms; this is true for toxoplasmosis, parvovirus, rubella and cytomegalovirus. The others may be asymptomatic in some instances but are better known for their well

described clinical syndromes, i.e. herpes simplex infection, varicella and syphilis.

Toxoplasmosis is a zoonosis caused by the protozoa *Toxoplasma gondii*[74]. Sources of this parasite include raw meat, soil and the feces of cats[74]. Infection in pregnancy can cause mild or severe disease including chorioretinitis, blindness, hearing loss (sensorineural), mental retardation and seizures[74]. In the US the birth prevalence is estimated to be about 1 per 1000[74]. Neither the American College of Obstetricians and Gynecologists (ACOG) or the UK National Institute for Health and Clinical Excellence (NICE) recommend screening for antibodies to the condition but rather recommend measures to prevent acquisition, such as cooking meat to a safe temperature, washing fruits and vegetables, hand washing prior to handling food, wearing gloves during and washing hands after gardening or working with soil and avoiding handling of cat feces[75,76]. Screening for antibodies has been advocated in France prior to pregnancy to identify those at risk with the purpose of targeting education on modes of prevention[74] especially since congenital infection has been documented to occur with periconceptional infection[77]. In addition, preconceptional testing has been advocated as an aid to the diagnosis of congenital infection[78]. Nevertheless, given the controversy about testing in pregnancy, it may be premature to advocate widespread testing in the prepregnancy period. Education regarding modes of transmission has been recommended as one strategy to decrease the incidence of this congenital infection[79,80]. There are as yet, however, no data supporting the role of this education prior to pregnancy, and the amount of emphasis to be given to these educational interventions might be limited[81,82]. This could also apply to other conditions in which education is promoted as an intervention such as listeriosis and CMV.

Syphilis, a sexually transmitted infection caused by the spirochete, *Treponema pallidum,* which causes significant disease in the mother and infant[83]. Initial stages are often asymptomatic and lead to latent syphilis in the mother[83]. When passed to the fetus, a possibility in up to 80% of pregnancies[84], infection can lead to prematurity and perinatal death[83]. The condition can be treated and its complications prevented through screening and treatment with penicillin[83]. In the US, screening has been advocated during pregnancy and prior to pregnancy for those at high risk[85]. It is estimated that worldwide 2 million cases of congenital syphilis occur each year, with 25% ending in pregnancy loss (stillbirth or miscarriage) and 25% with serious infection or low birth weight[84]. The current global strategy calls for testing and treatment in pregnancy of women and their partners, as well as screening those at high risk, such as patients in sexually transmitted infection clinics some of whom might not be pregnant but are of reproductive age[83].

Parvovirus or fifth disease is associated with a rash, erythema infectiosum and non-specific symptoms of a viral syndrome[75]. About 50% of adults are immune to the disease in the US[86]; however, few data are available from low and middle income nations[87]. Among individuals with acute infection in pregnancy, only 4% are affected with fetal loss and hydrops fetalis as a consequence of fetal anemia; most cases have healthy outcomes[88]. Parvovirus infection has not been associated with mental retardation or congenital anomalies[86]. Antibody levels for parvovirus are recommended for the evaluation of stillbirth[89], as these have been reported in up to 7–15% of stillbirths in some European-based series[87]. There are no specific recommendations for testing for antibody status prior to pregnancy or for counseling for prevention other than recommending routine hand hygiene[6].

Rubella, German measles, is the quintessential and historical preconceptional intervention. Vaccination for this condition has as its primary aim the prevention of congenital rubella syndrome (CRS). The infection causes mild disease in children and adults, whereas

in affected fetuses it can cause CRS characterized by deafness, cataracts, microcephaly, mental retardation, cardiac defects, liver and spleen damage, and bone lesions[90]. Since the introduction of the vaccine in the US in 1969, the incidence of the syndrome has declined by 99%[91]. WHO currently recommends two strategies for the incorporation of rubella vaccine in national immunization programs, as either a targeted approach for women of reproductive age or, where good vaccine coverage (>80%) can be assured, universal childhood vaccination, with the aim of eliminating rubella and congenital rubella[47]. (If rubella vaccination is performed on a wide scale, it is most typically in a combination vaccine with mumps, which does not cause congenital infection but is associated with spontaneous abortion.) Since rubella vaccination coverage is not always universal, one recommended preconceptional test is to check the rubella status especially in groups emigrating from countries with low rates of rubella vaccination[41].

Cytomegalovirus infection in pregnancy can cause a variety of symptoms in the affected fetus including hearing loss, mental retardation, cerebral palsy, chorioretinitis, growth restriction, hepatosplenomegaly, thrombocytopenia, jaundice and anemia[75]. More severe disease is more likely with primary infection but can occur in cases of secondary infection[92,93] and has been reported following infection occurring either before or shortly after conception[94]. Some authors recommend testing in the preconceptional period to focus prevention efforts on those at risk for primary disease[95], although others question the value of any screening program[96]. The prevention efforts recommended are those to prevent transmission from young children to adults through avoidance of personal contact and hygiene efforts to prevent contact with saliva and urine[97]. Examples include hand washing, especially after changing diapers or feeding young children, not sharing eating utensils or toothbrushes with young children and avoiding saliva when kissing young children[97]. Although some evidence supports education in seronegative pregnant women[98–100], at least one study suggested this intervention was not as effective among non-pregnant women[100] as those who were pregnant. Showing more promise, however, is a vaccine for CMV which has demonstrated efficacy in phase two randomized trials[101].

Two other herpes infections besides CMV can affect the fetus. Genital herpes simplex infection rarely causes congenital infection but when transmitted vertically during childbirth it can lead to herpes, a devastating CNS infection or disseminated disease[102]. Thus, vertical transmission is the subject of most prevention efforts[102]. Like CMV, primary infection in pregnancy is associated with worse outcomes than secondary infection[102]. In patients with genital herpes, if known to exist in pregnancy, strategies are undertaken to reduce transmission including prophylaxis in the last month of pregnancy and cesarean delivery in the presence of active genital lesions at delivery[102]. To date there are no recommendations to universally screen for herpes simplex virus (HSV) sero status in asymptomatic women either during or prior to pregnancy[102]. In contrast, recommendations suggest testing women whose partners have genital herpes with type specific antibodies and using measures to reduce the acquisition of HSV through daily antiviral therapy[103] and condom use[104].

Herpes zoster virus or varicella zoster virus (VZV), causes both varicella and zoster infection. Primary infection can lead to congenital infection[105]. Unlike herpes simplex, however, only primary infection is of concern, and a vaccine is available[105]. A high risk of severity exists for the mother if infection occurs during pregnancy including the development of varicella pneumonia[41]. Screening prior to pregnancy and in adults can be performed via a reliable history or, in the face of a negative history, with screening for VZV antibodies[105]. As the vaccine is a live attenuated virus, it

must be avoided in pregnancy, but its use in the preconceptional period has been recommended[41]. Currently the vaccine is not recommended for routine use by WHO[47], or in the UK as a routine in childhood or reproductive aged adults, where it is recommended in high risk individuals[106]. In the US, the vaccine is recommended in childhood. Adults, including women with no documented immunization, no prior infection or seronegative, if tested, are recommended to be vaccinated[107]. Women documented to be negative during pregnancy are recommended to be vaccinated in the postpartum period[107].

CHLAMYDIAL AND GONORRHEAL INFECTIONS

Infection by *Chlamydia trachomatis* is the most common bacterial sexually transmitted infection worldwide, with an estimated 92 million cases worldwide in one 1999 estimate[108,109]. Gonorrheal infection was estimated to have 62 million incident cases in the same year[109]. Both cause cervical infection which can lead to pelvic inflammatory disease (PID), chronic pelvic pain and infertility[108,110]. Outcomes of pregnancy include ectopic pregnancy and, in neonates, eye infection and specific to Chlamydia, pneumonia, and to gonorrhea, disseminated gonococcal infection (sepsis, arthritis, meningitis) or scalp abscess (if a fetal scalp electrode is used in the setting of maternal gonorrhea)[108,111]. It is estimated that 1000–4000 newborns worldwide are left blind owing to untreated ophthalmia neonaturum as a consequence of Chlamydia or gonorrhea[112]. Some of these cases are preventable, especially those due to gonorrhea, with the use of silver nitrate or antibiotic ointment eye prophylaxis; in contrast, those due Chlamydia are not[111].

Chlamydia is largely asymptomatic in men, considered carriers of the disease[108], and often asymptomatic in women (70–90%); screening those at high risk for infection has been recommended to decrease the burden of disease[113]. Many recommendations rest on the findings of randomized trials which demonstrated a decrease in PID in screened versus unscreened populations[114,115]. However, issues regarding trial design and results from observational studies have led to questions about the magnitude of benefit of screening programs[116]. Those at high risk in developed countries with access to highly sensitive testing (women less than age 25 and women over that age with multiple sex partners or a new sex partner or those with a history of sexually transmitted disease) are recommended to be screened[111,117]. Women in pregnancy at high risk also deserve screening[76,111,117], in part because the prevalence of neonatal infection (conjunctivitis and pneumonia) has decreased with widespread screening[111]. Direct randomized trial data supporting this recommendation are lacking[118].

Gonorrhea, unlike Chlamydia, is largely symptomatic in men but similar to Chlamydia is frequently asymptomatic in women[111]. In the UK, asymptomatic individuals are not screened in part because the disease is less prevalent and complications are less common; targeted interventions may have a role in groups at an especially high risk such as inner city residents, those attending clinics for sexually transmitted infections, and men who have sex with men and others[119]. In the US, the US Preventive Health Task Force cites fair evidence to screen asymptomatic pregnant and non-pregnant women at high risk, including women under age 25 and those with new or multiple sex partners[120]. The task force also cites the potential for prevention of preterm labor and chorioamnionitis as a rationale for screening in pregnancy[120].

Studies in Africa have shown a high prevalence of Chlamydia infection in pregnancy ranging from 9 to 13%, and in Asia rates vary from 6 to 27%[109]. Gonorrheal prevalence in pregnancy in Africa varies widely from less than 1% to 8%[109]. In areas where access to

testing is limited, a syndromic approach to screening pregnant women for these infections is recommended[118]. Efforts to control Chlamydia and gonorrhea globally involve screening women who are commercial sex workers and their partners[121]. Some evidence suggests that screening and treating Chlamydia and gonorrhea may help prevent the acquisition of HIV[121]. Women in the preconceptional period at high risk who are screened and who have these infections may benefit from a reduction of their sequelae for themselves, their pregnancy and their newborns.

HEPATITIS B AND C

Hepatitis B and C are caused by viruses and can lead to chronic liver inflammation[122,123]. Both are transmitted from infected blood – from receiving a transfusion with the virus present (uncommon where testing of blood is performed), intravenous drug use/unsafe injection practices, vertical transmission at birth and as a sexually transmitted infection[122,123]. In developing countries sources of infection for hepatitis B also include early childhood infections through close contact with infected household contacts where, along with vertical transmission, these account for a majority of cases[122,124]. Because acute infection with viruses is often either asymptomatic or associated with non-specific symptoms, many individuals are unaware they are infected unless tested[122,123].

Hepatitis B is very common; worldwide estimates count 2 billion as infected, 350 million living with chronic infection and 600,000 dying from complications of hepatitis[125]. Death occurs from either cirrhosis or liver cancer[125]. The risk of chronic disease is age dependent – 90% of those who contract it in infancy (0–1 year), 30–50% of children and 10% of adults progress to develop chronic disease[125]. If chronic disease develops as a child, the risk of complications is high, with about 25% eventually developing cirrhosis or liver cancer[125]. The primary focus of hepatitis B in preconceptional care involves vaccination to prevent vertical transmission, which can occur at variable rates from as low as less than 10% to as high as 70–90% in the absence of any prevention measures, depending on the pattern of the chronic infection[126]. Currently hepatitis B vaccine is recommended in childhood shortly after birth and in adults previously vaccinated who are at high risk[47]. Other recommendations for preconceptional care include testing those at high risk for hepatitis B carrier status, instructing them on avoidance of transmission to uninfected individuals including information on the prevention of vertical transmission[41]. Some patients with hepatitis B may undergo treatment of long duration[127] in which case their reproductive life plan and adequate contraception should be considered before embarking on therapy.

Hepatitis C is also common, with an estimated 123 million people worldwide being infected[128]. Major modes of transmission in developed nations are injection drug use and in undeveloped nations unsafe therapeutic injections and transfusions[128]. Unlike hepatitis B, infection through sexual contact and perinatal transmission is much less efficient and thus represents a smaller source of hepatitis C infection[128]. HIV infection along with alcohol use are also important co-factors in the global burden of disease associated with hepatitis C[128]. As the risk of vertical transmission is low (4%, although it is 2–3 times higher in those with HIV) and most children are asymptomatic and have no sequelae, there are no recommendations to screen pregnant women or to perform cesarean delivery or other specific interventions to prevent such infection[123,129]. Current preconceptional recommendations include screening those at high risk of the

disease to inform them of the risks of transmission and the disease course[6]. Similar to hepatitis B, treatment for hepatitis C is long term and includes ribavarin[130] which is contraindicated in pregnancy. A woman undergoing treatment should have her reproductive life plan reviewed and have appropriate contraception[6].

CONCLUSION

Infections comprise a significant burden of disease for women of reproductive age and their neonates. A great many can be prevented through immunization, with many vaccinations being recommended in childhood. For others, early detection and treatment, if indicated, in the preconceptional period may benefit not only the mother, but also her children as well. These interventions and strategies represent a doubling of effect since at least two individuals are frequently the beneficiaries of preconceptional care.

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SECTION 3

Previous pregnancy events

17

Recurrent pregnancy loss

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DEFINITION

Recurrent pregnancy loss (RPL) refers to the consecutive loss of three or more clinically recognized pregnancies prior to the 20th week of gestation (excluding ectopic, molar and biochemical pregnancies). RPL is classified into two categories: primary RPL, which consists of repeated miscarriages in which a pregnancy has never been carried to viability; and secondary RPL, in which a live birth has occurred at some time. Secondary RPL confers a better prognosis than primary RPL[1].

INCIDENCE

About 10–15% of all clinically recognized pregnancies end in miscarriage. Approximately 2% of women experience two and 0.4–1% of women experience three consecutive losses[2]. At less than 6 weeks' gestation the risk of miscarriage ranges from 22 to 57%, it declines to 15% at 6–10 weeks and 2–3% after 10 weeks of gestation[3].

RISK FACTORS AND ETIOLOGY

Couples with pregnancy loss usually express concern regarding the cause and risk of recurrence. The risk of miscarriage increases with maternal age and parity, being 19% at less than 35 years and increasing to 47% in those over 35 years. In a similar fashion, the risk of miscarriage increases from 14–21% after one miscarriage to 24–29% after two and 31–33% after three pregnancy losses. The minimum diagnostic workup of couples experiencing RPL consists of a complete medical, surgical, genetic and family history and a physical examination (see below).

General causes of RPL are shown in Table 1.

GENETIC FACTORS

The highest rate of cytogenetically abnormal fetuses occurs earliest in gestation, with rates declining after the embryonic period (>30 mm crown–rump length (CRL)).

Table 1 General causes of recurrent pregnancy loss

Causes	*Percentage* (%)
Genetic factors – chromosomal abnormality	3–5
Primary miscarrier (no live births)	7
Secondary miscarrier (1 or more live births)	50
Anatomic causes	5–10
Immune mechanisms	50
Thrombophilias	10–13
Endocrine	20
Infection	1
Unexplained	15

Parental chromosomal abnormalities

In approximately 3–5% of couples with RPL, one of the partners carries a balanced structural chromosomal anomaly (versus 0.7% of the general population), the most common being balanced reciprocal (60%) and Robertsonian (40%) translocations.

Aneuploidy

The risk of aneuploidy (meiotic non-disjunction, polypoid from fertilization abnormalities) increases as the number of previous miscarriages increases.

Other

Progesterone receptor gene polymorphism may play a role in RPL and is an active area of investigation[4]. Maternal diseases including sickle cell anemia, myotonic dystrophy, Marfan's syndrome, homocystinuria, factor VIII deficiency, dysfibrinogenemia and Ehler's Danlos syndrome are all associated with increased fetal loss.

Investigations and treatment

Couples with a history of RPL should have peripheral blood karyotyping, and cytogenetic analysis of the products of conception should be performed if the next pregnancy fails.

Genetic counseling can provide the couple with a prognosis for future pregnancy, as well as offer familial chromosomal studies and appropriate preimplantation genetic diagnostic procedures in future pregnancies. In addition, the couple should be informed that they have a 40–50% chance of a healthy live birth in future untreated pregnancies following natural conception.

ANATOMIC CAUSES

Acquired and congenital uterine abnormalities are responsible for 10–15% of RPL[5] and may be associated with fetal growth restriction and preterm delivery.

Uterine anomalies

The most frequent uterine defects include septate, bicornuate and didelphic abnormalities. The septate uterus is most common and associated with the poorest reproductive outcome (miscarriage rate more than 60% in untreated cases)[6,7]. Other anatomic causes of RPL are diethylstilbestrol exposure related anomalies, Asherman's syndrome, leiomyomas and endometrial polyps. A primary endometrial receptor defect appears to be responsible for RPL in some patients.

Investigation and treatment

Transvaginal ultrasound is useful for making a diagnosis of uterine anomalies[8]. Hysteroscopy is usually reserved for patients in whom intrauterine pathology is suspected and operative hysteroscopy is necessary. Transvaginal ultrasound assessment of the cervix during pregnancy may be useful in predicting preterm birth in cases of suspected cervical weakness. Magnetic resonance imaging (MRI) is useful for distinguishing between a septate and bicornuate uterus[8].

Cervical incompetence

No satisfactory objective test is available for cervical incompetence, and diagnosis is usually made on the basis of a history of late miscarriages, preceded by spontaneous rupture of membranes and painless cervical dilatation.

Investigation and treatment

The Medical Research Council (MRC)/Royal College of Obstetricians and Gynaecologists (RCOG) trial of elective cervical cerclage reported a small decrease in preterm birth and delivery of very low birth weight babies, the benefit being most marked in women with three or more recurrent second trimester miscarriages[9]. However, no significant improvement in perinatal survival was present.

IMMUNE MECHANISMS

Both autoimmune and alloimmune mechanisms have been proposed as explanations for RPL.

Antiphospholipid syndrome

Antiphospholipid antibodies (aPL) are present in 15% of women with RPL and 33% of women with systemic lupus erythematosus (SLE)[10]. In women with RPL associated with untreated aPL, the live birth rate may be as low as 10%. Primary antiphospholipid syndrome (APS), which predominantly affects young women, refers to the association of aPL and adverse pregnancy outcome or vascular thrombosis. Adverse pregnancy outcomes include three or more consecutive miscarriages before 10 weeks' gestation; one or more morphologically normal fetal loss after 10 weeks' gestation; and one or more preterm birth before 34th week of gestation due to severe pre-eclampsia, eclampsia or placental insufficiency. When APS exists in chronic inflammatory disorders, such as SLE, it is referred to as secondary APS.

Investigation

To diagnose APS, it is mandatory that the patient have two positive tests at least 6 weeks apart for either lupus anticoagulant or anticardiolipin antibodies (aCL) of IgG and/or IgM class present in medium or high titers. In detection of lupus anticoagulant, the dilute Russell's viper venom (dRVVT) test is more sensitive and specific than the kaolin clotting time (KCT) or activated partial thromboplastin time (aPTT).

Treatment

Currently, several well controlled studies show that future live birth is significantly improved from 50% to 80% when a combination therapy of low dose aspirin (75 mg) plus heparin (5000 U once or twice a day) is prescribed. A recent randomized trial reported a high success rate with aspirin alone but included women with low titers of aPL only[11].

Antithyroid antibodies

Patients with treated thyroid dysfunction have no risk of increased miscarriage[12]. Although more women with RPL have antithyroid antibodies than in the general population, evidence that these antibodies actually cause pregnancy loss is lacking[13].

Investigation and treatment

Because several studies report an increased rate of fetal loss in women with high serum thyroid peroxidase (TPO) antibody concentrations, we propose that it should be investigated in women with RPL.

Current data suggest that in women with RPL and thyroid antibodies, treatment with L-thyroxine and/or prednisolone should be considered, although further controlled studies are essential[14].

Antinuclear antibodies

A connection exists between antinuclear antibodies (ANAs) and recurrent miscarriages, with a titer of over 1:40 causing concern.

Investigation and treatment

Measuring antinuclear and anti-dsDNA antibodies is not recommended as part of an evaluation of women with RPL.

Treatment with low dose prednisolone could be considered as a treatment modality in patients who have raised ANA, but further studies are needed.

Alloimmune factors

Allogeneic factors may cause RPL by a mechanism similar to that of graft rejection in transplant recipients. Human leukocyte antigen (HLA) sharing is a condition in which the normal process that allows for creation of maternal blocking antibodies in pregnancy is decreased. However, no clear evidence as yet proves an association between RPL and HLA incompatibility between couples.

Cytokines and miscarriage

Thomas Wegmann first proposed the immunotrophic hypothesis suggesting that a successful allo-pregnancy was a T helper 2 (Th2) phenomenon and demonstrating a Th2 cell cytokine profile response in normal pregnancy[15,16]. Since then a number of human and animal studies[17–20] further confirm the Th2 cytokine predominance associated with a successful pregnancy, although some controversy exists[21,22]. The apparently harmful Th1 cytokines, which can activate natural killer (NK) cells into lymphokine-activated killer (LAK) cells, include tumor necrosis factor (TNF)-α, interleukin (IL)-2, interferon (IFN)-γ, IL-12 and IL-18; the main Th2 type cytokines include IL-3, granulocyte macrophage colony stimulating factor (GM-CSF), CSF-1, IL-10 and transforming growth factor (TGF)-β[23,24]. A study published in 2008 demonstrated that women with a history of unexplained recurrent failed *in vitro* fertilization (IVF) treatment not only have a Th1 bias but also that this polarization is enhanced following hormonal manipulations that accompany IVF treatment[25].

It is as yet unclear as to what should be the proportion of the Th1 cytokines at the fetomaternal surface to either damage or benefit any ongoing pregnancy[26–28].

Role of other markers/substrates

In a study measuring serum concentrations of macrophage inhibitory cytokine (MIC)-1 in asymptomatic women at 6–13 weeks' gestation who subsequently miscarried or who had already miscarried, MIC-1 concentrations were a third of those in women who had ongoing pregnancies, an observation which suggested a possible predictive as well as therapeutic potential for MIC-1[29]. Recurring miscarriages also have shown an association with elevated serum homocysteine concentrations in other studies[30,31].

Natural killer cells and miscarriage

NK cells comprise about 10–15% of peripheral blood lymphocytes. Two distinct subsets of human NK cells are possible, depending on the cell surface density of the CD56 molecule. Approximately 90% of peripheral blood human NK cells are CD56dim and express high levels of FcγIII (CD16) as well as perforin. In contrast, a minority (approximately 10%) of NK cells are CD56bright and CD16dim. These CD16dim cells are the primary source of NK cell derived cytokines and thought to

be an important regulatory subset[32,33]. In the uterus, the NK cells form the largest population of the leukocytes and are predominantly the CD56bright variety.

Studies suggest that uterine NK cell function in preimplantation endometrium is to promote angiogenesis, and thus provide a potential mechanism by which the increased endometrial uterine NK cell density causes miscarriage by the final common pathway of excessive oxidative stress[34,35].

NK cell receptor expression

An imbalance between inhibitory and activating receptor expression is present in women with implantation failures[36]. When compared with normal controls, CD158a and CD158b inhibitory receptor expression by CD56dim/CD16+ and CD56bright/CD16− NK cells was significantly decreased, and CD161 activating receptor expression by CD56+/CD3+ NK cells was significantly increased in women with implantation failures[35]. In another study, infertile women had a significantly higher expression of NK cell activation markers of the CD69+ type[37].

NK cell cytotoxicity

Aoki *et al*. reported increased preconceptional NK cell activity in women with unexplained RPL[38], while other studies revealed that infertile women have higher levels of activated NK cells compared with control multiparous women and that women with elevated levels of activated NK cells have a poorer IVF treatment and pregnancy outcome[39,40]. In summary, despite a few contradictory studies[41,42] a significant amount of data points to increased peripheral or local NK cell activity contributing towards the pathogenesis of recurrent miscarriage.

NK cell numbers

An abnormal increase in peripheral blood NK cell parameters (either in NK cell absolute values or in proportion (%) prior to conception or during early pregnancy) is associated with recurrent miscarriage and infertility with multiple implantation failures[40,43]. Data suggest that there may be a significant difference in subpopulations among uterine NK cells, with a greater proportion of cells being CD56dim, which may have important functional implications. Some studies using CD57 monoclonal antibodies (mAb) demonstrated elevated NK cell populations in decidua[44,45], whereas studies using CD56 failed to document change[46,47].

Investigation

Specific immunological testing should be conducted as a part of ongoing research in a specialized center. This includes NK cells (number and activation), MIC-1, Th1 and Th2 cytokines, HLA typing, mixed lymphocyte antibody tests and mixed lymphocyte culture reactions.

Treatment

In the absence of strong data to prove the immune-endocrine nature of abnormalities in recurrent miscarriage, most of the clinical therapies used over the years have been of an empiric nature.

Progesterone In a subgroup analysis of three trials involving 91 women with recurrent miscarriages, progestogen treatment significantly decreased the miscarriage rate compared with placebo or no treatment[48]. Despite this the current RCOG Guideline No. 17 (published in 2003) states that there is insufficient evidence to evaluate the effect of progesterone or human

chorionic gonadotropin supplementation in pregnancy to prevent a miscarriage[49].

Heparin Heparin, in addition to its anticoagulant effects, suppresses NK cell cytotoxicity and antagonizes IFN-γ action by inhibiting its binding to the cell surface[50].

Prednisolone therapy A recent study by Thum *et al.* demonstrated that prednisolone has a similar *in vitro* suppression effect on NK cell cytolytic capability to intravenous immunoglobulins (IV)[51]. In addition, Xu *et al.* showed that prednisolone had a suppressive effect on TNF-α (Th1 cytokine) production from placental tissue[44]. Furthermore, Quenby *et al.*[35] reported that prednisolone could suppress NK cell levels and reduce the miscarriage rate in women with a history of recurrent miscarriage.

IV immunoglobulins Women with a history of recurrent miscarriage have a higher level of NK cell cytotoxicity which can be suppressed by co-culture of the NK cells with immunoglobulin-G (IVIg)[45]. However, women who have elevated NK cell cytotoxicity and a history of recurrent miscarriage or recurrent failed implantation during IVF may have a better obstetric outcome if they have IVIg infusion during IVF treatment or early pregnancy[52,53].

TNF-α inhibitors, sildenafil and 1,25-dihydroxyvitamin D3 Winger *et al.*[54] used mAb directed against TNF-α along with IVIg to improve pregnancy rates in their IVF patients. Concerns about such use, however, relate in part to an increased risk of infectious diseases, especially tuberculosis.

Evans *et al.*[55] demonstrated that several components of vitamin D metabolism and signaling are strongly expressed in human uterine decidua from first trimester pregnancies, suggesting that locally produced 1,25-dihydroxyvitamin D3 may exert immunosuppressive effects during early stages of gestation.

A study in 2008 by Jerzak *et al.*[56], evaluating the effects of vaginal sildenafil on NK cell activity, suggested that NK cell activity was significantly decreased after vaginal sildenafil therapy in the study women.

THROMBOPHILIAS AND FIBRINOLYTIC FACTORS

Retrospective studies have suggested an association between inherited thrombophilic defects, fetal loss and late pregnancy complications, with a presumed mechanism being defective placentation and microthrombi in the placental vasculature. Inherited thrombophilias include factor V Leiden, protein C and S deficiency, antithrombin III deficiency, activated prothrombin C resistance (APCR), methylene tetrahydrofolate reductase (MTHFR) C677T and G20210A prothrombin gene mutation. Acquired thrombophilia includes anticardiolipin antibodies and lupus anticoagulant.

In the absence of treatment, factor V Leiden is associated with an increased risk of miscarriage, compared with a normal factor V genotype. Factor V Leiden is carried by 5% of Caucasians, but is rarely found among Blacks. Other inherited thrombophilias are rare, and no conclusive studies have been conducted to prove their causality in RPL. Moreover, RPL has no significant association with plasminogen activator inhibitor-I4G/5G polymorphism or increased plasminogen activator inhibitor activity[57]. Procoagulant microparticles were shown to be associated with early and late unexplained pregnancy loss in one pilot study[58].

Investigations and treatment

A full inherited and acquired thrombophilia screen is recommended in women with RPL.

The general approach is to treat women with thrombophilia with a combination of low dose aspirin and low molecular weight heparin. Therapy may need to be started before pregnancy occurs and continued to 6 weeks after birth (see also Chapter 9).

ENDOCRINE

Endocrine factors may be responsible for 15–20% of RPL.

Polycystic ovarian syndrome

Women with polycystic ovarian syndrome (PCOS) have a miscarriage rate of 20–40% as compared to the general obstetric population (10–20%). This may be related to elevated serum luteinizing hormone (LH) levels, high testosterone and androstenedione concentrations, or insulin resistance[59].

Investigation and treatment

Day 2–5 follicle stimulating hormone (FSH), LH, prolactin, sex hormone binding globulin, prolactin and transvaginal ultrasound are the recommended investigations in women with recurrent miscarriages.

Pre-pregnancy suppression of high LH by either clomiphene or metformin among ovulatory women with RPL and PCOS does not improve the live birth rate.

Luteal phase defect

It is controversial as to whether such a defect exists and whether it is related to miscarriage.

Investigation and treatment

Diagnosis of luteal phase defect based on endometrial biopsy is not predictive of fertility status, and single or multiple progesterone levels are not predictive of future pregnancy outcome[60].

Treatment with progesterone supplementation does not have a beneficial effect on pregnancy outcome.

Diabetes

Diabetic gravida with hemoglobin A1c levels in the first trimester of more than 8 are at increased risk of miscarriage and fetal malformations.

Investigation and treatment

Routine screening for diabetes with the oral glucose tolerance test in asymptomatic women with RPL should not be performed unless a random glucose value is elevated.

Diabetic women with RPL should be treated in a multidisciplinary joint diabetic clinic.

Hyperprolactinemia

Normal circulating levels of prolactin may play an important role in maintaining pregnancy.

Investigation and treatment

A study of 64 hyperprolactinemic women with RPL randomly assigned subjects to therapy with bromocriptine or no therapy[61]. Treatment to lower prolactin concentrations was associated with a higher rate of successful pregnancy (86% versus 52%). Prolactin levels during early pregnancy were significantly greater in women who miscarried[61].

Thyroid disease

Poorly controlled thyroid disease (hypo- or hyperthyroidism) is associated with infertility

and pregnancy loss. Excess thyroid hormone increases the risk of miscarriage[62].

Investigation and treatment

Routine screening for abnormal thyroid function tests should not be performed in asymptomatic women. Women with overt thyroid disease should be referred to a specialist.

INFECTION

Some infections, including listeriosis, toxoplasmosis, cytomegalovirus and primary genital herpes, cause sporadic pregnancy loss, but no infectious agent has been proven to cause RPL[63].

Investigation and treatment

Routine cervical cultures for *Chlamydia* or *Mycoplasma*, vaginal evaluation for bacterial vaginosis and TORCH (toxoplasma, rubella, cytomegalovirus and herpes simplex) serology are not useful in the evaluation of RPL, but they may be indicated by patient history.

Screening for and treatment of bacterial vaginosis in early pregnancy in women with a history of second trimester miscarriage or preterm labor may reduce the risk of RPL.

OTHER CAUSES

Chemicals

Chemicals which have been associated with RPL include nitrous oxide, arsenic, aniline dyes, benzene, ethylene oxide, lead, pesticides, mercury and cadmium.

Personal habits

The association between RPL and smoking, alcohol use or caffeine consumption is unclear[64].

Decreased ovarian reserve

Women with unexplained RPL have a higher incidence of elevated day 3 FSH and estradiol levels than women with known causes of RPL.

Day 1–3 FSH or a clomiphene challenge test can be considered in women of any age with RPL. A day 3 FSH level of less than 15 mIU/ml and high estradiol levels more than 80 pg/ml are associated with reduced oocyte numbers.

UNEXPLAINED

A significant proportion of cases of RPL (15%) remain unexplained, despite detailed investigations. These women can be reassured that the prognosis for a successful pregnancy outcome with supportive care alone is in the region of 75%. Treatment offered to couples with unexplained RPL includes the following:

- *Lifestyle modification* Weight loss, exercise, avoiding alcohol, caffeine intake and smoking.
- *Progesterone* Large randomized controlled studies demonstrating the efficacy of progesterone treatment are lacking, but the drug is widely prescribed to women with RPL.
- *IVF and preimplantation genetic diagnosis (PGD)* Studies evaluating the value of IVF in women with RPL have yielded mixed results. A combination of IVF and PGD at the 6–8 cell stage appears promising[65].
- *Oocyte donation* Ovum donation can overcome the problem of poor quality oocytes and has been associated with a live birth rate of 88% in women with RPL[66].
- *Combination therapy* A recent observational study compared 50 pregnant women treated before and during pregnancy with prednisolone (20 mg/day), progesterone (200 mg/day), aspirin (100 mg/day) and folate (5 mg/day) with 52 women who were not treated; the first trimester pregnancy loss rate was 19% in the treated and 63% in the untreated group. Although this difference was not statistically significant, it is clinically important and perhaps resulted from insufficient study numbers[67].
- *Complementary therapies* Many acupuncturists report success in treating women with a history of RPL. Dietary supplementation with vitamin B complex, including folic acid and co-enzyme Q10 may suggest a reduction in RPL. Reflexology, a holistic therapy, attempts to relieve stress, pain and muscle tension and thus help to reduce miscarriages.

BIOCHEMICAL PREGNANCY LOSS

A biochemical or pre-clinical pregnancy loss is defined as loss of a biochemically evident pregnancy before it is identifiable on ultrasound.

Early pregnancy loss occurs in 75% of all pregnancies, out of which 15–20% are clinically recognized. However, the true rate of early pregnancy loss is close to 50%, because of the high number of chemical pregnancies that are not recognized in the 2–4 weeks after conception. In a classic study by Wilcox *et al*. in 1988[68], 221 women were followed up during 707 total menstrual cycles. A total of 198 pregnancies were recorded; 43 (22%) were lost before onset of menses and another 20 (10%) were clinically recognized losses.

Investigations

No investigative studies have been conducted on the recurrent biochemical pregnancy loss.

A US study on 122 women experiencing IVF implantation failure with a negative pregnancy test and 20 women with chemical pregnancy loss evaluated aPL, ANA and elevated NK cells[69]. Women with chemical pregnancies had a higher frequency of aPL than women with implantation failure associated with a negative pregnancy test. The prevalence of ANA and NK cells did not differ between the two groups. The authors concluded that the mechanisms involved in chemical pregnancies may be the result of defective angiogenesis as compared to pregnancies with a negative pregnancy test which involve implantation failure.

Treatment

As not much work has been done on the diagnosis and treatment modalities of chemical pregnancies, it is a very challenging area of reproductive medicine. A short trial of low dose prednisolone could be the way forward in the treatment of recurrent miscarriage, especially as the safety of prednisolone is well established. High quality data on management of biochemical RPL are limited and, therefore, therapeutic intervention is largely guided by the underlying cause.

CONCLUSION

RPL is an emotionally traumatic experience for a couple. Multidisciplinary teams expert in managing patients with RPL should coordinate evaluation and management. These should include gynecologists, geneticists, rheumatologists, hematologists, immunologists and reproductive specialists. High quality data on management of RPL are limited; therapeutic intervention is largely guided by the underlying cause of RPL. In all cases, emotional support is important in caring for these anxious couples.

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18
Previous fetal death

Bode Williams and Sujata Datta

INTRODUCTION

Fetal death is a tragedy that causes severe distress to parents and caregivers. Parents want to know why their baby died and the chance of recurrence in future pregnancies. In the immediate postnatal period, they need extra emotional support in addition to appropriate information about the sequence of pregnancy events. Of great importance, they want all their questions answered in a timely fashion.

The obstetrician and his/her fellow health-care providers must make every attempt to identify the cause(s) of fetal death, as providing this information will improve the parents' understanding of events and may aid in grief resolution. At the first follow-up visit, the health-care provider (preferably an obstetrician or physician) should review the pregnancy events and have all relevant documents available for discussion and review. Postnatal test results and future reproductive options including contraception and lifestyle changes should be discussed as appropriate. If it might be of general or specific use, or if the parents request it, genetic counseling should be offered and the management plan for the next pregnancy should be discussed.

This chapter discusses investigations required to establish the causes of a fetal death after 20 weeks' gestation and outlines strategies to improve the chances for a successful subsequent pregnancy.

DEFINITION AND INCIDENCE

There is no standard definition for fetal death. Many countries define fetal death according to gestational age for legislation and statistical purposes[1]. As a result of such differences in definition, it is not possible to directly compare international fetal death rates.

In the United States, for example, intrauterine fetal death refers to fetal death after 20 weeks' gestation[2]. In England and Wales, on the other hand, intrauterine fetal death or stillbirth refers to fetal death after 24 weeks' gestation. Thus, the fetal death rate after 20 weeks' gestation in the United States was reported as 6.23 per 1000 total births for the year 2003[2]. In England and Wales in 2007 the stillbirth rate after 24 weeks was 5.2 per 1000[3,4]. In clinical practice, however, the evaluation of causes of fetal death is the same irrespective of the definition.

EVALUATION OF FETAL DEATH

The causes of fetal death can be subdivided into maternal, fetal, placental/cord and external factors. In some cases, fetal death may be the result of a combination of causes. In a significant number of cases, the cause(s) of death will remain unexplained in spite of extensive investigations[5–7].

Common causes of fetal death

- Maternal conditions: sepsis, diabetes and pre-eclampsia

- Fetal conditions: malformations, chromosomal and genetic disorders, infection, growth restriction and hydrops
- Placental and cord complications: abruption, infarction, tight knot in the cord and abnormal umbilical cord coiling[8]
- Fetomaternal conditions: fetomaternal hemorrhage
- Contributory (and in some instances external) factors: maternal obesity, drug misuse, advanced maternal age >40 years, social deprivation, trauma, uncontrolled medical problems including thyroid disease, cholestasis, antiphospholipid syndrome and inherited thrombophilia[3,5,9–11].

Checklist of potential procedures to be initiated after diagnosis of fetal death

- Parents should be given the opportunity to see and hold their baby and keep items of remembrance if they wish, as this may help with grief resolution[12]
- The nature of all postnatal tests should be fully explained to the parents
- Written information should be provided and the parents should be given ample time to arrive at a decision(s) if required
- Parents should be informed that their baby will be treated with care and respect during the postmortem examination. If they wish, the body will be returned in a suitable condition for viewing and further disposition after the examination
- In some countries, the UK being a prime example, parental consent must be obtained for placental histology, postmortem examination and photographs of the fetus[13]
- Parents should be encouraged to choose the funeral arrangement appropriate to their needs
- All relevant health-care professionals involved in the pregnancy care should be notified and future clinic appointments should be canceled.

History and review of medical records

In most cases of fetal death, the exact cause will not be apparent on clinical presentation. A targeted history should therefore be taken to determine the cause of death.

The pregnancy dating must be verified to exclude fetal growth restriction. In addition, enquiries should be made about specific pregnancy complications such as fever, rash, hypertension, diabetes (pre-existing and gestational), vaginal bleeding, genital tract infections and prelabor rupture of membranes. The timing and duration of exposure to any medications, including drug and alcohol misuse during pregnancy should be recorded. A family history of genetic, chromosomal and congenital malformations in both parents and any sibling should be elicited. All relevant medical records regarding any pre-existing illness should be obtained whenever possible. All antenatal test results including any abnormal findings should be noted.

All events surrounding the fetal death must be recorded clearly and accurately in chronological order. This will ensure that parents are given consistent information and will be useful in the management of subsequent pregnancies.

Investigations

The optimum tests for the evaluation of fetal death remain controversial and a direct cause of death will be found in only in 50–75% of cases[5,6,14–16].

External examination of the stillborn fetus

A detailed external examination of the stillborn should be performed with a description of all normal features and any obvious abnormality. Photographs of the fetus and close up views of any specific abnormalities should be obtained[17], as they will provide useful information at follow-up appointments.

The fetal body weight should be obtained in addition to other body measurements, including the foot length (which may be useful in confirming gestational age before 23 weeks' gestation), and head, chest and abdominal circumferences which may help exclude fetal growth restriction[18].

Postmortem examination of the fetus and placenta

Parents should be informed that a postmortem examination is the most informative test, as postmortem examinations reveal the cause and timing of fetal death in 40–50% of cases[14,19–26]. Some common postmortem findings include fetal abnormalities, fetal infection, fetal hypoxic injury, umbilical cord complications, placental dysfunction, infection, tumors and infarction.

Of great importance, in 20–40% of cases the postmortem, combined with other tests, will provide information regarding recurrence risk and management of the next pregnancy[19,23,25,26].

Even if no specific cause is identified, a negative postmortem result is still helpful in counseling parents about the list of fetal and placental conditions that have been excluded[27].

A full postmortem examination should include fetal chromosome culture with or without DNA analysis, X-ray (if indicated), magnetic resonance imaging (MRI) (if fetal examination is declined), and, finally, gross, microbiological and histological examination of the fetus and placenta[18].

Mandatory maternal tests

Full blood count

This is an important baseline test that helps dictate further management in the acute phase, especially in the presence of vaginal bleeding, placental abruption, pre-eclampsia, ruptured membranes or chorioamnionitis.

Glycosylated hemoglobin

This test can exclude poor glycemic control as a cause of fetal death in women with unrecognized gestational and pre-existing diabetes[28,29].

Kleihauer

This test determines the presence of significant fetomaternal hemorrhage, a silent but not uncommon cause of fetal death. In rhesus (D) negative women, this test also can determine whether sufficient anti-D has been given[30,31].

Anti-red cell antibody serology

This test excludes immune hemolytic disease. In cases of fetal hydrops, it should be repeated in the postnatal period even if the previous antenatal screen was negative, as some women develop atypical red cell antibodies late in pregnancy[32–34].

Maternal serology for viral and parasitic infection

Serological testing for cytomegalovirus (CMV), toxoplasmosis, herpes simplex and parvovirus B19 should be performed to exclude congenital viral infection associated fetal death[35–38]. Rubella serology should be repeated in non-immune women[39]. Serological testing for

syphilis should be repeated if the test was not performed in pregnancy or in women with history of sexually transmitted infection and those who live in endemic areas[40].

Bacteriology

Appropriate culture samples including vaginal and cervical swabs, placental swabs and fetal swabs should be obtained to exclude congenital bacterial infection. If the mother is unwell, then blood cultures to exclude listeriosis and urine cultures should also be obtained[37,41]. The bacterial organisms commonly found on culture in association with fetal death include group B streptococcus, *Escherichia coli*, *Chlamydia* and *Ureaplasma urealyticum*, *Haemophilus influenza*, *Klebsiella* spp, coagulase negative staphylococcus and *Enterococcus faecalis*, among others[42–44].

Selective tests

Parental chromosome and DNA analyses

These examinations should be considered if there is evidence of fetal chromosome rearrangement abnormalities or a suspicion of a fetal genetic disorder[18,45,46].

Coagulation profile

Coagulation profile testing is indicated if there is vaginal bleeding, the dead fetus is retained in the uterus for more than 2–3 days or the patient opts for expectant management. A slow decline in the plasma fibrinogen level is expected after the dead fetus has been retained in the uterus for more than 4 weeks, although abrupt changes in the coagulation system have also been reported a few days after fetal death[47,48].

Renal, thyroid and liver function tests and bile salts

These tests are indicated if there is a clinical suspicion of pre-eclampsia, sepsis, cholestasis and thyroid problems[49,50].

Urine toxicology

Urine toxicology is indicated if substance abuse is suspected[51].

Blood film for malaria parasites

This is indicated in endemic regions or for those with a history of travel to these areas[52].

Maternal thrombophilia screen

The link between maternal thrombophilia and fetal death is controversial. If, however, evidence of placental vascular thrombosis and infarction is present, then antiphospholipid screen (lupus anticoagulant and anticardiolipin antibodies) and inherited thrombophilia screen (factor V Leiden mutation, prothrombin gene mutation antithrombin III, protein C, protein S deficiency and hyperhomocysteinemia) are indicated[53–56].

Maternal autoantibody screen

If fetal hydrops or endomyocardial fibroelastosis is found at postmortem, maternal blood should be tested for the presence of anti Ro and anti La antibodies to exclude pre-existing autoimmune disease[57].

Maternal alloimmune antiplatelet antibodies

Analysis for maternal alloimmune antiplatelet antibodies is indicated in the presence of fetal hemorrhage at postmortem[58].

Figure 1 provides an example of a simple, structured fetal death outcome form for collating test results. It can be used to provide parents and clinicians with relevant clinical information at the follow-up visits and will be relevant in future pregnancies.

Date of delivery: Gestational age at delivery: Birth weight: Gender:

MOTHER

Blood tests
HbA1C (glycosylated):
FBC: Hemoglobin: Platelet:
Clotting profile: PT and APTT: Fibrinogen:
Blood group: Rhesus: Atypical red cell antibody:
Kleihauer:

Biochemistry
Renal, thyroid, liver function tests, bile salts:

Serology
Toxoplasmosis
Rubella
Cytomegalovirus
Parvovirus B19
Syphilis

Antiphospholipid screen
Anticardiolipin antibody
Lupus anticoagulant

Bacteriology
High vaginal swab
Chlamydia swab
Listeria
Urine culture
Blood culture
Urine toxicology

Inherited thrombophilia screen
Protein C Protein S
Anti thrombin III Factor V
Prothrombin Homocysteine
Autoantibody screen
Anti-Ro Anti-La
Alloimmune antiplatelet antibody
Anti-HPA 1a antibody

PLACENTAL

Gross examination:
Cultures:
Maternal side:
Fetal side:
Histology:

FETAL

Gross external examination (specify abnormality):

Photographs:

Postmortem:

Chromosomes/DNA studies:

X-ray/MRI findings:

Ear, nose and throat swabs culture:

GENETICS

Parent chromosomes/DNA studies: Mother

Partner:

Summary:

Mother's age: Pregnancy complications:

Mode of delivery:

Cause of death (and mechanism if known):

Contributing factors:

Co-morbidity/pre-existing illnesses

Figure 1 Fetal death outcome form. HbA1C, glycosylated hemoglobin; FBC, full blood count; PT, prothrombin time; APTT, activated partial thromboplastin time; MRI, magnetic resonance imaging

EMOTIONAL SUPPORT

Pregnancy loss is an exceedingly stressful life event and may have short- and long-term adverse effects on the mental health of parents and existing children. Continuing emotional support and/or pastoral care should be provided to help families cope with and recover from the fetal loss. They also should be offered bereavement counseling and provided with written information regarding family support groups[59–61].

POSTNATAL FOLLOW-UP

A postnatal appointment should be organized when all test results are available. This appointment usually needs to take place 6–12 weeks after the sentinel event. At this visit, the pregnancy events and all circumstances surrounding the fetal death should be reviewed. An interval medical history should be obtained. In addition, specific enquiries should be made about contraception use, anxiety and depression symptoms and medication[61].

When discussing postnatal test results with the parents, it is important to explain the differences between specific cause(s) of death, contributory factors and any coincidental finding as this will affect the recurrence risk estimate and subsequent pregnancy care.

The couple must also be given ample opportunity to ask questions[12,59].

PRE-PREGNANCY EVALUATION AND PREGNANCY PLANNING

Specific measures

If a specific cause of death is identified, it may then be possible to estimate recurrence risks and identify interventions that could improve the chances of a successful subsequent pregnancy.

- If there is evidence of fetal chromosomal abnormalities, fetal structural malformations or suspicion of a genetic disorder, it may be necessary to check the parent's chromosomes with or without DNA analysis to exclude an inherited chromosomal or genetic abnormality[18]. In addition, parents should be referred to a clinical geneticist to discuss the likely recurrence risk of specific defects as well as future reproductive options, including prenatal diagnosis and management of subsequent pregnancy.
- Women with active chronic medical problems such as hypertension, diabetes, thyroid and autoimmune disorders have an increased recurrence risk of fetal death and other pregnancy complications. Ideally, chronic medical problems should be addressed, controlled and medications optimized prior to the next pregnancy[5,50]. Details of such plans are discussed in other chapters of this book.
- A history of fetal death and ischemic placental disease is associated with an increased recurrence risk of placental complications. In subsequent pregnancies, fetal growth should be monitored by serial third trimester ultrasound examinations[62,63]. The predictive value of uterine artery Doppler screening in the context of a previous fetal death is not known[64].

General measures

- Women should be advised to take supplemental folic acid to reduce the risk of neural tube defects (see Chapter 22)
- Women who have not had and thus are susceptible to rubella, hepatitis B and varicella should be vaccinated
- Women who smoke should be advised that smoking cessation before and/or during pregnancy leads to improved pregnancy outcomes[65]
- Women with alcohol and drug addiction should be referred to the appropriate agencies for intensive help directed to cessation or, in the worst case, moderation
- Maternal obesity is associated with increased pregnancy complication rates for both the mother and the fetus[66,67]. Obese women should be advised that weight loss would improve outcomes as well as enhance fetal monitoring in subsequent pregnancies
- Women with unresolved or complicated grief and signs of depression require additional support from appropriately trained health-care professionals. A psychiatric referral for counseling and treatment may be warranted[68,69].

Interpregnancy interval

- The optimum interpregnancy interval after fetal death remains unknown; however, normal bereavement generally resolves within 6–12 months in most instances[70,71]
- Couples should be advised to delay the next pregnancy until they feel emotionally capable of undertaking it[72].

Management of subsequent pregnancy

A history of previous unexplained fetal death confers a 2–10-fold increased risk of a repeat fetal death and a 4-fold increased risk of gestational diabetes in a second pregnancy when compared with women with previous uncomplicated pregnancies[64,73,74]. Such 'high-risk' women will therefore need specialist antenatal care, testing to exclude gestational diabetes and close supervision in subsequent pregnancies[63,64,73–77].

Fetal monitoring

There is no evidence that intensive fetal monitoring reduces the risk of fetal death in future pregnancies. Serial third trimester ultrasound examinations are commonly used to identify poor fetal growth which may precede fetal death[9,64]. In addition, serial ultrasound examinations may help reassure parents with heightened anxiety levels that fetal growth is satisfactory[64,78,79].

Timing of delivery

Elective induction at term in subsequent pregnancies does not increase live birth rates. Depending on the timing of previous fetal death, however, many obstetricians offer elective delivery after 37 weeks to allay parental anxiety and avoid the risk of sudden fetal death[75,79]. Additionally, elective delivery at term gives parents some element of control over their pregnancy outcome.

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19

Prior pelvic inflammatory disease, endometriosis and ectopic pregnancy

Joyanto Choudhury and Saikat Banerjee

The aim of pre-pregnancy counseling is to address issues regarding women's concerns about their ability to fall pregnant and to give birth to a healthy baby at the end of pregnancy.

Pelvic inflammatory disease (PID)[1] and endometriosis[2] are both risk factors associated with subfertility and thus could potentially lead to failure to become pregnant. In the event of a successful conception, tubal damage secondary to these pre-existing disease processes increases the risk of an ectopic pregnancy. Of great importance, a prior history of an ectopic pregnancy is a possible indicator of existing tubal damage and hence a strong risk factor for reoccurrence[3]. Such an event will not only be associated with an unsuccessful pregnancy, but also with maternal morbidity at the very least, if not mortality. Even in the presence of first-world medical facilities, ectopic pregnancy still remains the leading cause of maternal mortality in the first trimester, with three women dying in the UK[4] and 45 in USA every year[5].

With the development of early pregnancy assessment units, screening for risk of ectopic pregnancy, one of WHO's primary objectives[6], not only is possible, but also has been shown to be cost effective[7]. It is therefore imperative to use the opportunity, when meeting a potential mother to be, to identify risk factors for ectopic pregnancy and to decide upon a management plan in advance for possible complications that may arise.

PRIOR PELVIC INFLAMMATORY DISEASE

PID is defined as an infection of the endometrium, fallopian tubes and/or contiguous structures caused by the ascent of microorganisms from the lower genital tract[1]. The majority of cases in young women are associated with sexually transmitted infections (STIs), the most prevalent being *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. These organisms often initiate an inflammatory process and then are replaced by opportunistic bacteria including aerobes, anaerobes and *Mycoplasma* sp[8]. Special consideration should be given to tuberculosis which is discussed separately in this book.

The Department of Health and Human Services in the USA[9] and the Department of Health in the UK[10] have expressed concerns that with changes in lifestyle, STIs represent a growing problem with nearly 333 million curable cases occurring worldwide annually[9]. This concern is not only based on increasing numbers of new STIs diagnosed in genitourinary clinics, but also on the fact that these rates are highest in women who are young and in the reproductive age range. Young women aged 16–25 years account for nearly half of all STIs diagnosed in genitourinary clinics, and it is this same group that will potentially be considering a pregnancy post-infection. Of further concern is the

fact that 15% of women rarely or never use a condom with a new sexual partner[9].

Prior infection (symptomatic or asymptomatic) is a risk factor for current infection, which may be associated with vaginal discharge, irregular vaginal bleeding or pelvic pain, all of which direct women to seek medical advice. Unfortunately, such infections can also be asymptomatic and thus undetected at the time of consultation in the absence of routine screening procedures. Pre-pregnancy counseling sessions may provide one of the few times that an otherwise healthy woman voluntarily accesses medical attention, and, as such, becomes an ideal chance to opportunistically screen for STIs.

For women with no prior history of infection, the current UK national antenatal care guidelines published by the National Institute of Clinical Excellence (NICE)[11] state that there is no good evidence to suggest that routine antenatal screening for STIs (other than HIV, syphilis and hepatitis B) is indicated. Previously, however, with the advent of the National Chlamydia Screening Programme[12], NICE had envisaged that based on current expert opinion, women who are pregnant or seeking pre-pregnancy counseling at the age of 25 years or younger, should be advised on the availability of the screening program and that screening could be undertaken as part of this program. In the USA routine antenatal screening is recommended for chlamydia along with gonorrhea, the latter if the pregnant woman comes from an area of high prevalence[13]. Referral screening programs also have the additional benefit of contact tracing.

Chlamydia

Chlamydia trachomatis is currently the most common curable STI in the western world. In current screening programs, 8.5% of women below 25 years of age test positive for chlamydia[14]. The clinical implications of chlamydia infection in pregnancy are identical to those outside pregnancy, with development of repeat PID, increased risks of subfertility and ectopic pregnancy. Approximately 70% of pregnant and non-pregnant women infected with chlamydia are asymptomatic; a small proportion may present with non-specific symptoms including vaginal discharge, dysuria, lower abdominal pain, postcoital bleeding or arthritis. The vaginal discharge may be mild, irritating, usually yellow, and often goes unnoticed. Therefore, in the presence of these symptoms, women in the clinic should be offered a test to exclude the possibility, with appropriate treatment and counseling if the result proves positive.

Asymptomatic chlamydia infection during pregnancy is associated with adverse pregnancy outcomes (low birth weight, preterm delivery and preterm rupture of membranes) as well as with postpartum endometritis and neonatal morbidity, including respiratory tract infection and conjunctivitis[15]. Up to two-thirds of women affected with chlamydia during labor may transmit the organism to the infant during vaginal delivery. The infection clearly is treatable and therefore is not an indication for cesarean section; no evidence links chlamydia with chorioamnionitis.

Microbiological detection is by vaginal, urine or blood tests (Tables 1 and 2). Nucleic acid amplification tests (NAAT) have a higher sensitivity (90–95%) than enzyme immunoassays (40–70%) and therefore are the recommended laboratory test for diagnosing chlamydia infection from endocervical and vulvovaginal swabs[16]. The vulvovaginal swabs have a sensitivity similar to endocervical swabs (90–95%) and can be taken by either the patient or health-care worker. Variable sensitivities (65–100%) have been reported using the first catch urine (FCU) specimen. Cell culture can be used on all specimen types, but has low sensitivity (60–80%); because it requires expertise and is costly, it is not recommended for routine purposes. On the other hand, the

Table 1 Tests in asymptomatic women. (Modified from UK National Screening and Testing Guidelines, 2006[16])

Site or specimen	*Gonorrhea*	*Chlamydia*	*Syphilis*	*HIV*
Urethra				
Cervix	Culture	NAAT		
Vagina		NAAT		
Rectum				
Oropharynx				
Urine		NAAT		
Blood			EIA/TPPA/TPHA+VDRL	EIA

NAAT, nucleic acid amplification test; EIA, enzyme immunoassay; TPPA, *Treponema pallidum* particle assay; TPHA, *Treponema pallidum* hemagglutination assay; VDRL, Venereal Disease Research Laboratory

Table 2 Tests in symptomatic women. (Modified from UK National Screening and Testing Guidelines, 2006[16])

Site or specimen	*Gonorrhea*	*Chlamydia*	*Syphilis*	*HIV*
Urethra	M+C		DGM	
Cervix	M+C	NAAT		
Vagina	NAAT	NAAT		
Rectum	Culture	Tissue culture		
Oropharynx	Culture	Tissue culture	PCR	
Urine		NAAT		
Blood			EIA IgM	EIA/LIA

M+C, microscopy + culture; DGM, dark ground microscopy; PCR, polymerase chain reaction; EIA, enzyme immunoassay; LIA, line immunoassay

direct fluorescent antibody test is applicable to all specimens, including rectal and pharyngeal swabs, but its widespread use is hampered by a low sensitivity (80%) and the need for technical expertise; it is therefore not recommended for routine diagnosis.

Diagnosis may also be made at surgical inspection of the pelvic and abdominal cavities with the demonstration of classical peritubular adhesions (Figure 1a) as compared to the central midline adhesive disease more commonly associated with endometriosis (Figure 1b).

The tubal fimbrial ends are often damaged, giving rise to distal occlusion with clubbing and mild hydrosalpinx. Such hydrosalpinges can be identified on transvaginal ultrasonography appearing as elongated paraovarian cysts containing multiple partial septae and an irregular inner luminal wall giving an appearance described as 'cog wheeling'. The cog wheels are a result of aggregation of the tubal luminal cilia (Figure 2). The fallopian tubes are usually bilaterally affected. At laparoscopy, the pathognomonic feature of prior chlamydial pelvic infection is that of perihepatic adhesions named Fitz-Hugh-Curtis syndrome which is also seen with prior gonorrheal infection and less commonly with tuberculosis associated PID.

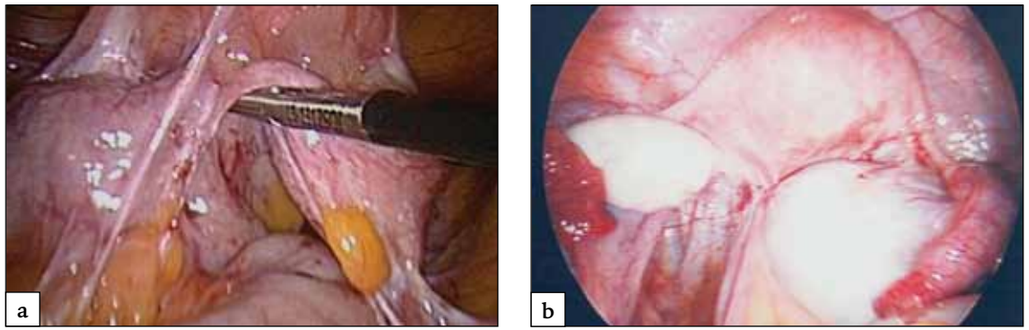

Figure 1 (a) Fine filmy peritubular adhesions associated with pelvic inflammatory disease. (b) Dense central adhesions of the posterior cul de sac associated with endometriosis (note the tubal sparing)

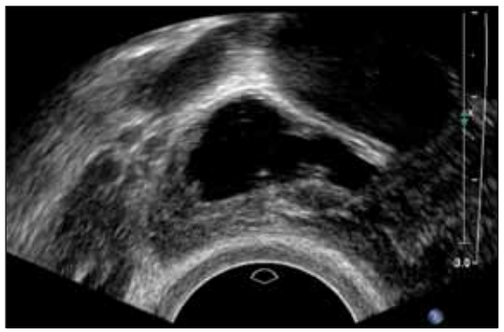

Figure 2 Hydrosalpinx on transvaginal ultrasound (cog wheel)

The recommended antibiotic therapy for genital chlamydia infection (Table 3) in non-pregnant women is doxycycline (100 mg twice daily for 7 days) or azithromycin (1 g single dose). Alternative agents are erythromycin (500 mg four times a day for 7 days) or ofloxacin (200 mg twice daily for 7 days). Doxycycline and ofloxacin are contraindicated in pregnancy. The safety of azithromycin in pregnancy and lactating mothers has not yet been fully assessed, although available data indicate that it is safe[17]. Recommended therapeutic alternatives in pregnancy and breastfeeding are erythromycin or possibly amoxicillin (500 mg three times a day for 7 days). A test of cure is not routinely recommended but should be performed in pregnancy or if non-compliance or re-exposure is suspected. It should be deferred for 5 weeks (6 weeks if azithromycin is given) after treatment is completed in order to avoid false positive results[16].

Pre-pregnancy treatment of the tubal damage is by surgery to divide adhesions and possibly open up the distal blocked end of the fallopian tube by a cuff salpingostomy. An anti-adhesive barrier may be employed as recurrence of disease and tubal re-occlusion is high (25–50%)[18], forcing couples to later resort to *in vitro* fertilization (IVF) therapies.

The evidence is limited regarding treatment of chlamydia around pregnancy as well as its effectiveness in reducing the incidence of preterm rupture of membranes, preterm delivery and low birth weight babies. Current studies are of poor quality[19–23]. Cohen *et al.*[20] compared the clinical outcomes in pregnant women with proven cervical chlamydia infection successfully treated with erythromycin 500 mg four times a day for 7 days ($n = 244$) against those who remained chlamydia positive throughout pregnancy ($n = 79$) and chlamydia-free matched controls ($n = 244$) in a low-income indigenous urban pregnant population considered at high risk. The successfully treated group had a significantly lower frequency of preterm rupture of membranes (7.4% versus 20.3%), preterm contractions (4.1% versus 24.1%) and small for gestational age babies (13.1% versus 25.3%) when compared with

Table 3 Treatment and follow-up. (Modified from UK National Screening and Testing Guidelines, 2006[16])

	Treatment in non-pregnant patient	*Treatment in pregnancy*	*Test of cure*	*Follow-up period*
Chlamydia	Doxycycline 100 mg oral twice daily for 7 days; or azithromycin 1 g single oral dose	Erythromycin 500 mg oral four times a day for 7 days	In pregnancy only: 5 weeks after completing therapy	Asymptomatic: 6 months; Symptomatic: 4 weeks
Gonorrhea	Single dose: ceftriaxone 250 mg IM; or cefixime 400 mg oral; or spectinomycin 2 g IM	Same as non-pregnant		3 months
Syphilis	Early: single dose of benzathine penicillin G 2.4 MU IM; Late: 3x weekly doses	First and second trimester: Single dose of benzathine penicillin G; Third trimester: 2x weekly doses	Early: 1, 2, 3, 6, 12 months then 6 monthly until serofast; Late: 3 monthly until serofast	
Bacterial vaginosis	Metronidazole 400–500 mg oral twice daily for 5–7 days; or 2 g single oral dose	Same as non-pregnant		

the chlamydia persistent group. There was no such difference, however, when the successfully treated group outcomes were compared to the chlamydia negative group. The frequency of preterm birth was lower in the treated group compared to both the untreated group (2.9% versus 13.9%) and matched controls (2.9% versus 11.9%). There was no difference between the three groups regarding other pregnancy outcomes, including frequency of vaginal deliveries, cesarean section, postpartum endometritis, antepartum hemorrhage or stillbirth. These authors concluded that in a high risk group for chlamydia infection there are potential benefits with repeated prenatal chlamydia testing plus successful erythromycin treatment. However, three large studies in the general female pregnant population in 1985[21], 1990[22] and 1997[23], screened by rapid immunoassay antigen detection and treated with erythromycin failed to show any effect on pregnancy outcome, except when carried out in the third trimester.

The evidence remains difficult to evaluate in terms of neonatal effects. In situations where the link is obvious, such as in vertical infection transmission, rapid identification and proper management of the neonate is considered a clinical and cost effective alternative to screening. This is still considered an area of debate and research, especially for studies looking into treatment effects that reduce the potential harms of preterm birth and neonatal complications. If, however, the patient is symptomatic, then the outlook is altered in favor of treatment.

Gonorrhea

Genital infection with *Chlamydia trachomatis* accompanies genital gonococcal infection in up to 40% of women[24]. Undetected, untreated or inadequately treated gonorrhea is another important cause of upper genital tract infection in addition to facilitating the transmission

of HIV. Not unlike chlamydia, infection of the endocervix is often asymptomatic (in up to 50%). Symptomatic infection may present with altered vaginal discharge, lower abdominal pain, dysuria, menorrhagia or intermenstrual bleeding. Hematogenous dissemination may cause skin lesions, arthralgia, arthritis and tenosynovitis. Diagnosis is based upon identification of Gram-negative *Neisseria gonorrhoeae* by culture of specimen obtained from the endocervix and urethra (Tables 1 and 2). Culture offers a readily available, specific, sensitive and cheap diagnostic test that allows confirmatory identification and antimicrobial susceptibility testing. It is currently the method of first choice for use in genitourinary medicine clinics. Treatment comprises a trio of simultaneous activities: patient treatment, contact finding and treatment, and avoidance of unprotected sexual intercourse until both partners have completed treatment. Recommended antibiotics (Table 3) include ceftriaxone (250 mg IM single dose), cefixime (400 mg oral single dose) and spectinomycin (2 g IM single dose). Pregnant women should not be treated with quinolone or tetracycline antimicrobials. A microbiological test of cure is not routinely necessary. Pregnancy does not diminish treatment efficacy. There is no evidence base to support widespread unselected or selective community screening for gonorrhea in the USA[25] and UK[26].

Syphilis

This is caused by infection with *Treponema pallidum* and is an uncommon cause of pelvic infection *per se*, but in pregnancy the causative agent can cross the placenta to infect the fetus, thus resulting in congenital disease. Untreated babies can display physical deformities (saddle nose, frontal bossing, dental deformities, bowed legs), delays in development and seizures, along with many other problems. Of equal importance, maternal syphilis can also lead to serious adverse outcomes of pregnancy (80%) including spontaneous miscarriage, low birth weight babies, stillbirth and an increased risk of perinatal death[27].

Based on the recent increase in cases of infectious syphilis in the UK and USA, screening is recommended for all asymptomatic patients attending genitourinary clinics. Attendance at a pre-pregnancy clinic also provides an excellent screening opportunity. Furthermore, screening for syphilis should be offered to all pregnant women at an early stage in antenatal care because treatment of syphilis is beneficial to the mother and baby[9,11].

The diagnosis is based upon serological tests and direct detection of *Treponema pallidum* by dark ground microscopy in primary and secondary syphilis (Tables 1 and 2). *Treponema pallidum* enzyme immunoassays (EIA) that detect both IgG and IgM tend to be more sensitive in primary infection. The *Treponema pallidum* particle assay (TPPA) is recommended in preference to the *Treponema pallidum* hemagglutination assay (TPHA). TPHA can be used in combination with a cardiolipin antigen/reagin test, such as Venereal Disease Research Laboratory (VDRL) or rapid plasma regain (RPR), to maximize the detection of primary infection on screening[28].

The first line of treatment for infected individuals is benzathine penicillin G 2.4 MU intramuscularly. A single dose is adequate for early syphilis, whereas three weekly doses are recommended for late syphilis. In pregnancy, a single dose is optimum treatment in the first and second trimester, but two weekly doses are required in third trimester. Alternative treatment agents include azithromycin, ceftriaxone and doxycycline. Follow-up is essential to monitor cases of re-infection or relapse (Table 3). As is the case with most STIs, contact tracing and treatment is imperative not only for prevention of reinfection, but also for the health of the general population.

Bacterial vaginosis

The etiology of bacterial vaginosis is unknown. It commonly causes asymptomatic disease which can increase the risk of PID as well as adverse pregnancy outcomes including preterm rupture of membranes, preterm delivery and low birth weight babies[29]. It has been suggested that bacterial vaginosis is also linked to increased risk of acquisition of HIV, but further studies are required for accurate evaluation[30].

Diagnosis is based on the appearance of a Gram-stained smear according to the modified Ison-Hay scoring system. There is insufficient evidence regarding routine screening or treatment of asymptomatic pregnant and non-pregnant women to improve outcome. The recommended antibiotic for treatment in symptomatic bacterial vaginosis is oral metronidazole 400–500 mg twice daily for 5–7 days or 2 g single dose[31] (Table 3).

A past history of unexplained late miscarriage and/or preterm birth has been linked to bacterial vaginosis in early pregnancy[32], and hence may be considered as an indicator for screening in subsequent pregnancies[33].

Serological screening for hepatitis B virus and HIV infection should be offered to all pregnant women early in antenatal care because appropriate antenatal interventions can reduce mother-to-child transmission of infection[9,11]. This is discussed elsewhere in this book.

PRIOR ENDOMETRIOSIS

Endometriosis is defined as the presence of endometrium-like tissue outside the uterine cavity, the presence of which induces a chronic inflammatory reaction[2]. Common locations for such tissue include the ovaries, uterosacral ligaments and posterior cul de sac peritoneum.

Although endometriosis is a chronic condition thought to be potentially present at least from the time of menarche, it also has been identified in the female embryo[34]. This latter finding is recent and, if verified, may be important to future research efforts to understand the etiology of the condition. At present, the most popular theory, that is, retrograde menstruation and implantation[35], originally proposed over a century ago by John Albertson Sampson, tends to be repeated in textbooks, albeit with very little evidence, as it fails to account for the presence of distal metastasis except for implantation at operative scar sites after cesarean section, a well described but rare complication of this mode of delivery. Another theory with growing popularity is that of tissue metaplasia[36], but this is yet to be confirmed.

Endometriosis is said to involve 5% of the female population[37], with higher incidence found at laparoscopy when investigating for causes of subfertility (25–40%)[38] or pelvic pain (45–50%)[39]. Except in severe forms where resultant adhesions cause tubal damage, the causal link with subfertility is not well defined. It is thought that endometrial deposits may secrete cytokines within the pelvic cavity that may be cytotoxic to sperm and/or the embryo immediately or shortly after fertilization. The possibility of subfertility is the main concern in a pre-pregnancy clinic. During pregnancy there are few issues, and rarely endometriosis may be associated with worsening of pain due to adhesion stretching. More commonly, pregnancy leads to an improvement of endometriosis associated pelvic pain[40], and pregnancy was advised as a therapeutic methodology in the era before modern treatment modes. Having said this, becoming pregnant should not be considered as a long-term treatment option, as the effects usually are short term and confined to the length of the associated amenorrhea[41].

Evidence to date suggests endometriosis to be a complex trait influenced by both genetic and environmental factors. It has long been considered that endometriosis carries a genetic predisposition in many families, but despite extensive research no specific genes have been identified. Encoding genes for detoxification

enzymes GST (glutathione-S-transferase) and NAT2 (N-acetyltransferase 2) are thought to be responsible, but further studies are required to confirm such an association[42]. Higher levels of dioxin, an exogenous toxin, have been detected in the blood of women with endometriosis[43]. The peritoneal environment promoted by hormones, growth factors and cytokines, along with existing damage to the peritoneal surface by trauma, infection or inflammation, can contribute to an increased risk of disease development. Factors thought to be protective against development of endometriosis include current use of combined oral contraceptive pills, smoking and exercise[44].

The gold standard of diagnosis is surgical inspection[2], at either laparoscopy or laparotomy. Endometriosis is characterized by a variety of appearances which range from superficial transparent sago grain lesions, red or black lesions to deep fibrotic lesions of the peritoneum. Endometriotic cysts of the ovaries, occurring in up to 20% of cases[45], can reliably be diagnosed by community based transvaginal ultrasonography[46]. Using this technique, the positive likelihood ratio ranges from 7.6 to 29.8 and the negative likelihood ratio ranges from 0.1 to 0.4, thus establishing sonography as a good diagnostic test to either confirm or exclude this condition. Endometriotic cysts are colloquially known as chocolate cysts due to their hemoglobin content.

More recently, in highly specialist tertiary clinics, it has been possible to identify peritoneal disease on transvaginal ultrasound[47], transrectal ultrasound[48] and magnetic resonance imaging[49]. These are, however, not widely available in the community and most hospital based practices.

Despite the variable macroscopic appearances of endometriosis, the common linking feature of these lesions is that all display histological features of endometrial glands and stroma.

Expectant management is the first line treatment, as the ability to manage the condition medically and/or surgically is fraught with limitations. In a study by Mahmood and Templeton[50], women with suspected endometriosis underwent a diagnostic laparoscopy and staging. A repeat laparoscopic assessment at a mean interval of 12 months revealed that 27% of women had disease regression, whilst the disease was static in 9%, and 64% had worsening of the disease severity as defined by the rAFS (revised American Fertility Society) score. Treatment is therefore based on current symptomatology and not disease identification or suspicion. Although it may be thought that early stage treatment will protect against future disease progression and thus reduce the risk of future sub- or infertility, no evidence substantiates this theory, as the disease progression rate is unknown (it would require repeated surgical observation assessment), and the limited available data clearly identify spontaneous disease regression. Interventional treatment is not without risks which can result in a reduction in fertility with a risk of peritonitis and adhesion formation[51].

Medical management of this estrogen dependent condition involves estrogen suppression and thus ovulation suppression. Benefits only last for the duration of therapy, are limited by the adverse side-effects of the drugs, and are short lived following cessation of therapy[52]. The main indication for medical therapy, therefore, is pain management rather than subfertility.

Laparoscopic surgical management by excision or ablation is currently considered optimal management with concurrent treatment for subfertility[2,53]. In the presence of severe deep nodular disease careful prior counseling is required, as treatment is not without associated morbidity that can in itself adversely affect and delay pregnancy. In these circumstances, surgical treatment should be carried out by specialist centers of excellence. In the UK currently the British Society for Gynaecological Endoscopy (BSGE) has set out to identify such units (www.bsge.org.uk). In cases of severe

disease with tubal occlusion treatment may be by IVF. However, many IVF specialists require removal of endometriomas of 4 cm or more in diameter prior to treatment to improve ovarian drug response and reduce the complication of peritonitis by inadvertent puncture of the cyst during egg collection[53].

There are no known problems that can affect the fetus once conceived, except the risk of future susceptibility of female offspring if a genetic link is believed, as discussed earlier.

Endometriosis support groups available worldwide (www.endometriosis.org) play a vital role in improving awareness about the disease process and its common sequelae, particularly in relation to future fertility.

PRIOR ECTOPIC PREGNANCY

Ectopic pregnancy is defined as implantation of a fertilized ovum anywhere other than the endometrial lining of the uterus. Extrauterine implantation occurs most commonly in the fallopian tube accounting for 98.3% of all ectopic locations. Tubal implantation can be in the ampular region (79.6% of tubal pregnancies), the isthmic region (12.3%), at the fimbrial end (6.2%) or rarely in the interstitial region (1.9%)[3]. The less common sites of ectopic pregnancy are ovarian, cervical, cesarean scar and intra-abdominal. Heterotopic pregnancy, when an intrauterine and an extrauterine pregnancy occur simultaneously, is a rare condition with an incidence in spontaneous conception cycles of 1:30,000. However, this incidence has been slowly rising in recent years with the advent of assisted reproduction techniques and could range from 1:500 to 1:100 in IVF pregnancies[54].

There is a global rise in the incidence of ectopic pregnancy which is mainly attributed to the increasing incidence of PID[55]. In the UK around 11,000 cases are diagnosed per year (incidence 11.5 per 1000 maternities)[56], while in the USA 108,800 cases (incidence 19.7 per 1000 maternities) are reported annually. In Northern Europe the incidence of ectopic pregnancy is 18.8 per 1000 maternities[55]. In the last triennium (2003–05)[4] in the UK, 14 reported maternal deaths resulted from early pregnancy complications; ruptured ectopic pregnancies and subsequent hemorrhage accounted for ten of these deaths. In the USA ectopic pregnancy accounts for 9% of all pregnancy related deaths each year[55]. This outlines the serious implications of the condition.

Women with a prior ectopic pregnancy or those who are aware of its potential risk, possibly directed by the presence of predisposing risk factors[3] (Table 4), should be alert to its possibility in a future pregnancy and require both counseling and support at any preconception visit.

Classically, ectopic pregnancy presents with a triad of associated symptoms: (1) amenorrhea of 6 weeks, (2) abdominal pain (69.3%) and (3) vaginal bleeding (45.3%)[57]. However,

Table 4 Risk factors for occurrence of an ectopic pregnancy[3]

High risk
Tubal surgery
Sterilization
Previous ectopic pregnancy
In utero DES exposure
Intrauterine device use
Documented tubal pathology
Moderate risk
Infertility
Previous genital infections
Multiple sexual partners
Low risk
Previous pelvic or abdominal surgery
Cigarette smoking
Vaginal douching
Early age of intercourse (<18 years)

DES, diethylstilbestrol

diagnosis can be difficult, as clinical presentation is exceedingly variable, and some women (as many as one-third) are completely asymptomatic with absent risk factors. Hence the only way of ensuring that this potentially lethal diagnosis is never missed is that the clinician should always be aware of the probability and act to exclude the possibility, if there is any suspicion.

Early diagnosis is important to minimize morbidity, allow for different treatment options and maximize scope for future fertility. For these reasons, there exists a valid argument for offering ectopic pregnancy screening to women with known risk factors as soon as conception is confirmed with a positive urine pregnancy test. In view of the unpredictability and significant implications of the condition, it may even be considered that there could be a role for screening the entire pregnant population. In many ways awareness is one of the main objectives of early pregnancy assessment units in the form of secondary screening. However, although routine screening for ectopic pregnancy in the high risk population is not cost effective[58], it is undeniably good practice to offer women with a prior ectopic pregnancy an early pregnancy scan to confirm the location of the gestational sac. *It is axiomatic that ultrasonic findings of an empty uterus in a woman with a positive pregnancy test and clinical signs that might even remotely indicate ectopic pregnancy, receive follow-up by care-givers with sufficient understanding of the potential gravity of the situation to all concerned*. Moreover, the clinician has a duty to inform the woman attending the pre-pregnancy clinic of his/her concerns and the availability (or lack) of such resources locally, so that there is no unnecessary delay when the woman discovers she is pregnant.

Women with a family history of ectopic pregnancy may express concern regarding the chance of their having an ectopic pregnancy. They can be assured that there is no genetic predisposition to occurrence of ectopic pregnancy[59], but should be assessed individually to ascertain the presence of personal risk factors.

The diagnosis of ectopic pregnancy using ultrasonography is often by exclusion with the identification of an intrauterine pregnancy. This can usually be achieved as early as 4 weeks and 3 days of gestation by transvaginal ultrasonography (Figure 3) and a week later by transabdominal ultrasonography. Direct identification of the ectopic pregnancy by ultrasonography has an overall sensitivity of more than 90%[60] (Figure 4); in good units this is now considered the norm.

If the identification of an intrauterine sac is uncertain, the woman should be offered a serial transvaginal ultrasound assessment in 2–3 days, ideally by the same ultrasonographer. At this time the images should become more conclusive with the development of an intrauterine well defined hypoechoic cystic structure within one endometrial leaflet rather than the midline. It should also be spherical in outline and in one-third of cases may have a hyperechoic trophoblastic ring (Figure 3).

In women where a pregnancy cannot be identified, a diagnostic laparoscopy may be proposed if they are clinically compromised. Fortunately, the majority of such women, defined by Banerjee *et al.*[61] as women with

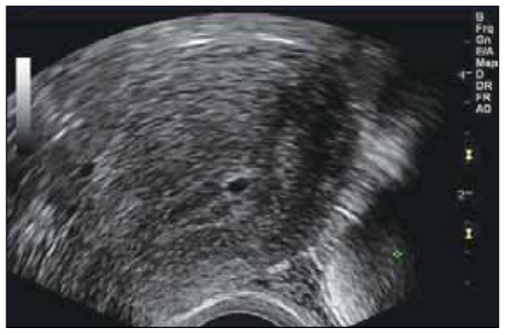

Figure 3 Transvaginal image of the sagittal section through an anteverted uterus along the midline. The hypoechoic cyst seen at the center of the endometrial cavity is consistent with an intrauterine pregnancy of 4–5 weeks' gestation

'pregnancies of unknown location', are clinically stable with minimal symptoms. In such women, serum hormone level estimation of human chorionic gonadotropin (hCG) and progesterone is a useful tool to identify and monitor for spontaneous resolution of the pregnancy, thus allowing attention to focus on those women with a potentially problematic diagnosis of ectopic pregnancy. Subsequent follow-up should be logical and individualized. The authors' current practice is to follow the protocol described in Table 5, which aims to reach a conclusive diagnosis in the safest possible way with minimum number of hospital visits.

If ectopic pregnancy is identified in a woman who is clinically stable and presenting initially for pre-pregnancy counseling, the therapeutic options include expectant, medical and surgical management.

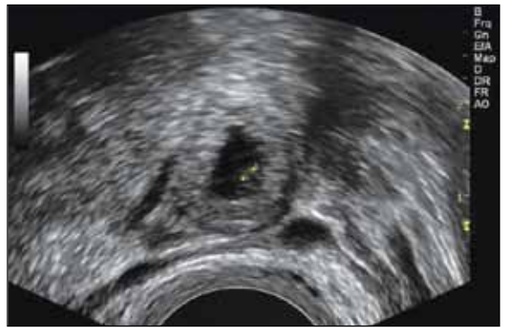

Figure 4 Transvaginal ultrasound image of an ectopic pregnancy

Expectant management has the obvious benefit of avoiding the risks associated with surgery. The success rate for spontaneous resolution varies between 25% and 88%, depending on the initial serum hCG level[62]. The subsequent intrauterine pregnancy rate following expectant management is 89%, whereas the risk of a recurrent ectopic pregnancy is 5%[56]. It is the authors' current practice to consider expectant management with initial serial hCG assays 48 hours apart and then at weekly intervals until serum levels are less than 20 IU/l[63] in women with a pregnancy that is not considered viable on ultrasound (absence of embryonic heart action or features not comparable to menstrual dates). As a predictor of success, one would expect a drop in serial hCG levels of greater than 66% within the first 48 hours and then more than 50% within 7 days, ideally with an initial hCG of less than 1000–1500 IU/l[56]. In a district general hospital setting, approximately 60% of ectopic pregnancies are successfully managed conservatively with no significant morbidity[64].

A reasonable alternative in clinically stable women with an initial hCG of less than 3000 IU/l is medical management. In the western world, this is increasingly becoming

Table 5 Protocol for management of 'pregnancy of unknown location' as defined by the absence of an intrauterine or extrauterine pregnancy on transvaginal ultrasound examination

Progesterone (nmol/l)	*hCG* (IU/l)	*Likely diagnosis*	*Management*
<20	>25	Resolving pregnancy	Repeat urine pregnancy test or serum hCG in 7 days
20–60	>25	Ectopic pregnancy or miscarriage requiring intervention	Repeat serum hCG in 2 days
>60	<1000	Normal intrauterine pregnancy	Repeat scan when hCG expected >1000 IU/l
>60	>1000	Ectopic pregnancy	Repeat scan same day by a senior examiner ± laparoscopy

hCG, human chorionic gonadotropin

an attractive treatment option and has been found to be cost-effective[65].

Medical management of ectopic pregnancy comprises a single dose methotrexate injection (systemic or local) at a dose of 50 mg/m^2. A small group of these women (14%) may require more than one dose of methotrexate, while around 10% will fail treatment, needing subsequent surgical intervention[56]. The success rate (defined as not requiring surgery) varies between 74% and 97% depending on the initial level of serum hCG rather than the size of the ectopic pregnancy[66]. After methotrexate therapy, 62–70% of women have a subsequent intrauterine pregnancy and 8% have recurrent ectopic pregnancy[62]. These values are almost identical to those obtained for expectant management.

In order to offer either non-surgical option, it is essential that the woman fully understands the risks discussed, particularly that of pregnancy rupture leading to hematoperitoneum and the need for emergency surgery. It is essential when offering such treatment regimens that there be appropriate local protocols with a 24/7/365 immediate access for medical reappraisal, should the clinical situation alter. If this is not possible or there is even a doubt about patient compliance, a surgical approach should be adopted as the first line treatment option.

Surgical management of ectopic pregnancy is still widely considered the first line of management in most countries worldwide. Surgery involves laparoscopy or laparotomy (if hemodynamically unstable) to perform either a salpingectomy (Figure 5) or salpingotomy (Figure 6). A meta-analysis of four cohort studies[63] suggested that there might be a higher subsequent intrauterine pregnancy rate associated with salpingotomy (Table 6), but the magnitude of benefit is small. This would need to be taken into consideration with the woman's desire for future fertility, the state of the unaffected contralateral fallopian tube, the additional morbidity associated with salpingotomy (small risk of tubal bleeding in the initial postoperative period), the potential need for further monitoring, and any treatment for persistent trophoblast (10%) as well as a risk of repeat ectopic pregnancy in future. Also under consideration would be the woman's wishes and availability of IVF services. After partial or total salpingectomy the rate of recurrent ectopic pregnancy is 7–10% as compared to 15% after salpingotomy[62].

The results of these studies have prompted the recommendation by the Royal College of Obstetricians and Gynaecologists (RCOG) in the UK[63] to consider laparoscopic salpingotomy as the primary treatment when managing a tubal ectopic pregnancy in the presence of contralateral tubal disease, whilst the evidence is not so clear when the contralateral tube is

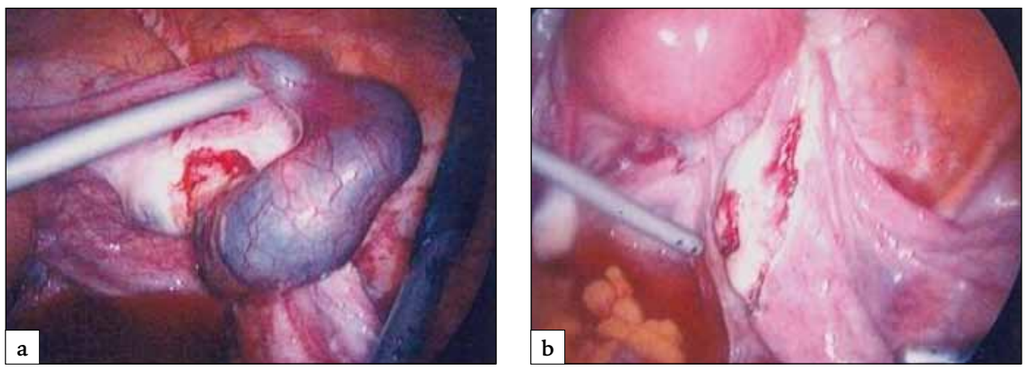

Figure 5 Laparoscopic salpingectomy ((a) before and (b) after)

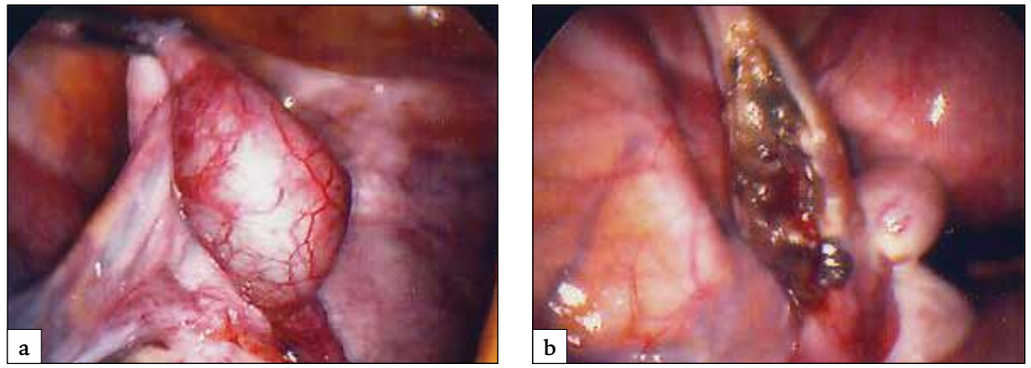

Figure 6 Laparoscopic salpingotomy ((a) before and (b) after)

Table 6 Intrauterine pregnancy rates following surgical treatment of tubal ectopic pregnancy[63]

	Salpingectomy (%)	*Salpingotomy* (%)
Silva *et al.*	54	60
Job-Spira *et al.*	56.3	72.4
Mol *et al.*	38	62
Bangsgaard *et al.*	66	89

healthy and future pregnancy is desired. In the latter circumstance the current accepted practice is towards that of salpingectomy.

Laparoscopy is superior to laparotomy irrespective of the type of tubal surgery, resulting in a higher rate of intrauterine pregnancy (77% versus 66%) and a lower rate of recurrent ectopic pregnancy (7% versus 17%). The cumulative pregnancy rate is also influenced by a history of infertility with an overall conception rate of 77% for all methods of treatment and a recurrence rate of 10%[62].

Age of the woman and prior history of infertility rather than a prior history of ectopic pregnancy should be the determining factor for considering IVF. Referral to an assisted conception unit may be considered in women with a history of recurrent ectopic pregnancies because of the concern of tubal subfertility. Screening for evidence of tubal patency may be performed either radiologically or at laparoscopy. However, patients should be made aware that with IVF there is an increased risk of recurrence of ectopic pregnancy and heterotopic pregnancy and that ovulation induction techniques can also lead to an increased risk of ectopic pregnancy (2.2% from IVF and 1.9% from intracytoplasmic sperm injection)[67]. Prophylactic salpingectomy after salpingotomy could be considered if there is evidence of hydrosalpinx in the affected fallopian tube, as it has been shown to increase the cumulative success rate of IVF[68].

In heterotopic pregnancies, the tubal ectopic is usually managed by salpingectomy as it is impossible to monitor for persistent tubal trophoblast implants with a simultaneous ongoing intrauterine pregnancy. The management of non-tubal ectopic pregnancies is outside the scope of this chapter.

Finally, all non-sensitized women who are rhesus negative with a confirmed or suspected ectopic pregnancy should receive anti-D immunoglobulin if managed medically or

surgically[63]. Furthermore, a previous ectopic pregnancy does not increase the risk of miscarriage (23%)[69] or any other adverse outcome in subsequent intrauterine pregnancies. Women who have had an ectopic pregnancy in the past or are concerned owing to the presence of risk factors may be aided further by the assistance and support of self-help groups (www.miscarriageassociation.org.uk).

SUMMARY

Women who present for pre-pregnancy counseling with a previous history or risk factors for pelvic infection, endometriosis or ectopic pregnancy require careful assessment as to the significance of the problem and its effects on the health of the woman both outside and during a future pregnancy, as well as the health of the potential future progeny. This is crucial even if only to reassure the woman that she is not at significant risk of serious problems. Pre-pregnancy assessment and correct advice will often avoid, if not limit, the potential complications that could arise as a result of these conditions.

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20

Preconceptional counseling of women with previous third and fourth degree perineal tears

Maria Memtsa and Wai Yoong

INTRODUCTION

More than 85% of women in the United Kingdom (UK) sustain some form of perineal trauma during childbirth[1]. In the majority of instances, only the perineal skin, vaginal epithelium and superficial muscles are involved, and such tears are only rarely associated with serious sequelae. Tears involving the anal sphincter, however, can have long-term impact on a woman's quality of life. Sultan[2] originally proposed the classification of obstetric anal sphincter injuries (OASIS) shown in Figure 1; this classification was later adopted by the Royal College of Obstetricians and Gynaecologists[3] and subsequently internationally accepted. A schematic representation of the anal sphincter is depicted in Figure 2. The prevalence of third and fourth degree tears appears to be dependent upon the type of episiotomy practised and thus varies considerably. In centers where mediolateral episiotomy is practised, the rate of OASIS is 1.7% (2.9% in primiparas), compared to 12% (19% in primiparas) in units that perform midline episiotomy[4].

This chapter describes the salient points that should be covered at the preconceptional consultation of a woman who has sustained a third or fourth degree OASIS. What this chapter does not cover specifically are the risk factors of anal sphincter injuries, evidence on how to prevent such injuries at first vaginal delivery, methods of repair of severe perineal tears and management of anal incontinence (whether surgical or medical).

First degree:	laceration of the vaginal epithelium or perineal skin only.
Second degree:	involvement of the perineal muscles but not the anal sphincter.
Third degree:	disruption of the anal sphincter muscles which should be further subdivided into:
	3a: <50% thickness of external sphincter torn.
	3b: >50% thickness of external sphincter torn.
	3c: Internal sphincter also torn.
Fourth degree:	a third degree tear with disruption of the anal epithelium as well.

Figure 1 Classification of perineal trauma

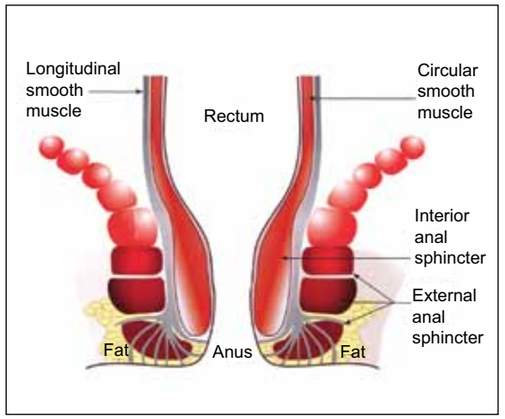

Figure 2 Schematic representation of the anal canal (modified from Sultan, Thakar and Fenner, 2009[4])

DIRECTED HISTORY FOLLOWING OBSTETRIC ANAL SPHINCTER INJURY

OASIS is associated with both short- and long-term sequelae to young, otherwise healthy women. Although the issue of anal incontinence (defined as the loss of normal control of bowel action leading to the involuntary passage of flatus and/or feces) predominates in the literature, it is by no means the only effect of anal sphincter damage. Pain, infection, dyspareunia and sexual dysfunction also may be present and play important roles in the woman's emotional and psychological well-being. This section describes the effects of OASIS on bowel function and the questions that should be asked in order to elicit the extent of the problem. An accurate description of the events leading to the injury and details of the repair are important and are most easily obtained by perusing the patient's prior delivery related notes. Unfortunately, these are not always sufficiently complete as to be truly informative. Anal incontinence, the main long-term effect of OASIS, can range from a minor leakage of feculant fluid, through occasional passage of stool during passage of flatus, to complete loss of bowel control.

Approximately 3–5%[5] of women experience fecal incontinence postpartum, but often are reluctant to discuss their symptoms. Bugg and colleagues[6] distributed questionnaires on urinary and anal incontinence to 275 primiparous women 10 months after delivery. Although up to 10% of women had developed new symptoms of fecal incontinence, the authors noted that only a small proportion had raised the issue with their doctor or midwife.

Because of the intimate nature of this topic, information is better obtained by a questionnaire rather than direct questioning. Specific inquiries that should be incorporated in the questionnaire include[7]:

- How often do you open your bowels per week?
- Is your stool hard or soft?
- Is your passage of stool painful?
- Do you strain excessively to open your bowels?
- Do you feel you emptied yourself completely?
- Is there any mucus or blood in the stool?
- Are you able to control your stool?
- Can you tell the difference between stool and flatus (wind)?
- Do you lose flatus when you do not mean to?
- Do you have any leakage of loose stool?
- How often do you have loose stool per week or day?
- Do you wear pads?
- Do you feel stool coming and you are unable to stop it? (urge incontinence)
- Do you feel it after it is too late? (true incontinence).

Women who have sustained OASIS should be assessed by a senior obstetrician and detailed debriefing of the circumstances surrounding

the delivery offered and any concerns explored. A genital examination should be performed, looking for scarring, residual granulation tissue and tenderness. At this point, specialist investigations organized to assess anal function, as alluded to in the next section, may be considered.

INVESTIGATION OF ANAL INCONTINENCE

In order to complement the information gained at history taking and physical examination, a number of investigations may be ordered. Some of these may not be available in a generalist setting and referral to a specialist center may be necessary. Prior to this, the pathophysiology of anal incontinence is briefly considered to better understand the choice of investigations.

Observational studies of women suffering from anal incontinence postpartum identified two types of insults: mechanical (i.e. relating to muscle/anal sphincters) and neuropathic (i.e. relating to the nerve supply of the muscles). Injury to the pudendal nerve (which innervates the anal sphincters) as it courses over the pelvic floor, may result in suboptimal continence. The effect of this type of insult is also thought to be cumulative and worsens with subsequent pregnancies. The evidence for the above observation comes from studies of women who had cesarean sections performed either electively or in early labor (control group) compared to women who had a cesarean section as an emergency in late labor[8,9].

The following tests help to assess the structure and the physiological function of the anal sphincter.

Anorectal manometry

Anorectal manometry[10] includes a series of measurements designed to establish:

- Deficits in anal sphincter function
- The presence or absence of rectoanal reflexes
- Rectal sensory function
- Defecatory function.

The apparatus consists of four components:

- An intraluminar pressure-sensing catheter
- Pressure transducers
- A balloon for inflation within the rectum
- The recording system.

No universally accepted standards exist for the equipment and/or the technique, unfortunately. Thus, it is difficult to compare data between centers, and it remains to each unit to develop its own normogram, preferably sex and age stratified. Anal sphincter function is assessed by identifying the functional anal canal length and by recording the maximum resting canal pressure and voluntary anal squeeze pressure. The length of the functional anal canal is shorter in incontinent patients than in control subjects; low resting anal tone is associated with passive anal incontinence, and low anal squeeze pressure correlates with symptoms of urge or stress fecal incontinence. Having said this, two potentially confounding factors operate in manometry: first, large diameter probes can distort the anal canal and falsely record high pressures; and, second, pressures in different areas vary at different levels of the anal cavity. Under these circumstances, calculated pressures should be averaged out.

The rectoanal contractile reflex (which can be assessed by manometry) is recruited at instances when the intrarectal pressure increases above the anal pressure. To prevent fecal leakage, the anal pressure should always exceed the intrarectal pressure; therefore, when increased intrarectal pressure is present, e.g. coughing, a multisynaptic response results in contraction of the external anal sphincter

maintaining the desired high anal pressure. In case of damage to the sphincter (whether structural or neurological), the reflex is lost and continence is compromised.

The purpose of assessing normal rectal sensation is to establish the ability of an individual to determine rectal distension and, therefore, the need to defecate. Rectal sensation may be quantified by using balloon distension, and the patient may be categorized into the rectal hypo- or hypersensitivity group. In general, it is believed that patients with rectal hyposensitivity may experience passive (overflow) incontinence, while hypersensitivity may present as urge incontinence. Anal manometry also allows the examiner to reproduce a situation simulating diarrhea by infusing large volumes of normal saline into the rectum. Accurate measurement of the volume of saline infused and leaked provides good evidence regarding rectal capacity and compliance. Patients with fecal incontinence are able to retain as little as 500 ml of saline compared to a normal subject whose rectum can hold over 1500 ml without any significant leakage.

Imaging of the anal sphincter

With the advent of detailed ultrasound and other imaging modalities, the radiologic depiction of the perineum and the anal sphincter complex has improved considerably over the years, and imaging is presently considered essential in the assessment and management of fecal incontinence, especially that related to obstetric trauma[11].

Imaging of the anal sphincters is achieved using an endoanal linear ultrasound probe and the different layers depicted are:

- Subepithelium, which is moderately reflective
- Internal anal sphincter, which shows low reflectivity
- Longitudinal layer, which is low to moderately reflective and consists of pubocervical fascia, smooth muscle from the longitudinal layer of rectum and striated muscle of the perineum
- External sphincter, which is of low to moderate reflectivity and can be divided into:
  - a subcutaneous part, which starts at the termination of the internal sphincter
  - a superficial part, which forms a complete ring around the anal canal
  - a deep part.

Figure 3 shows the normal four layer pattern of the anal canal on axial endosonography. Vaginal delivery affects sphincter morphology (even in the absence of OASIS); similar changes are not evident in pregnancy following elective cesarean section. Frudinger and colleagues[12] compared anal endosonography findings in nulliparous and age matched multiparous patients, demonstrating thinning of the anterior external sphincter with

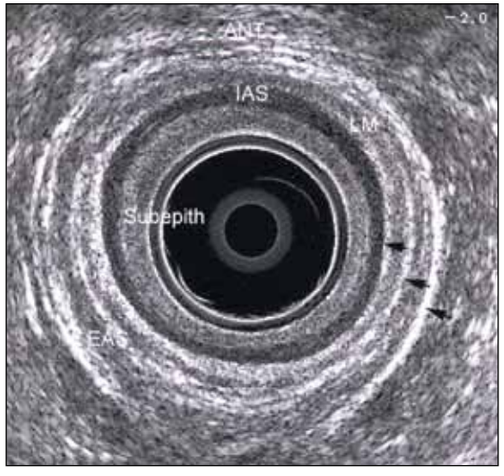

Figure 3 The normal pattern of the anal canal, as depicted by endoanal ultrasound. IAS, internal anal sphincter; EAS, external anal sphincter; ANT, anterior aspect; LM, longitudinal muscle

concurrent thickening of the longitudinal layer and the superficial external sphincter. These findings suggest diffuse trauma to the anus during delivery.

The use of anal endosonography has revolutionized the diagnosis of partial or small sphincter tears missed during clinical examination. A recent meta-analysis of tears demonstrated on ultrasound following 717 vaginal deliveries showed that the incidence of obstetric anal sphincter tears was as high as 26.9% in nulliparous and 8.5% for subsequent deliveries[13]. Injury of the external sphincter leads to formation of avascular scar tissue of uniform low reflectivity, which is easily detected on ultrasound as it crosses the planes.

The routine use of anal endosonography immediately after delivery has been investigated by Faltin and colleagues[14], who randomized 752 primiparous women with second degree lacerations into a control group which had conventional vaginal examination and a study group which was assigned to additional postpartum endoanal ultrasonography. Interestingly, 5.6% of women in the study group (who were thought to have second degree tears) were found to have sustained severe OASIS. Severe fecal incontinence (as assessed by Wexner Incontinence Score) was reported 3 months postpartum by 3.3% of women in the study group compared to 8.7% in the control and these effects persisted 1 year after delivery. However, ultrasonography needed to be performed in 29 women to prevent one case of 'missed' severe fecal incontinence, and five women would have had unnecessary intervention, as the defect was not clinically demonstrated.

Even though endoanal ultrasonography is considered the gold standard for the morphological assessment of the anal canal, the lack of volume calculations and relative patient discomfort limit its use in clinical practice. New methods that have been introduced include transvaginal ultrasonography (a reliable method with accuracy equivalent to that of the endoanal technique), transperineal ultrasound and endoanal magnetic resonance imaging (MRI). More recently, three-dimensional ultrasound has joined the field of pelvic floor imaging, and Valsky and colleagues[15] prospectively studied 117 primiparous women without clinically recognized third and fourth degree anal tears at 24–72 hours postpartum using this modality. They found that the internal sphincter was visualized in 100% of patients, while the external sphincter was fully visualized in only 84.6% of patients. Since three-dimensional ultrasound allows the digital storage of volume, employing this method shortens the examination time (mean examination time 3.5 min) and permits the visualization of the sphincter in the 'resting' state.

Pudendal nerve terminal motor latency

Prior to the advent of endoanal ultrasound, pudendal nerve electrophysiological studies were widely used in case of suspected incontinence, as it was believed that the majority of idiopathic or neurogenic fecal incontinence cases were due to pudendal neuropathy. Pudendal nerve terminal motor latency (PNTML)[10] measures the conduction time from stimulation of the pudendal nerve at the level of the ischial spine to the external anal sphincter contraction, with increased latencies being present in incontinent women following OASIS. However, the validity of the test has recently come under scrutiny, as both the sensitivity and specificity are poor and recent consensus advocates that the test should not be part of mainline investigations.

MANAGEMENT OF SUBSEQUENT PREGNANCIES

Figure 4 shows an algorithm for the management of women who had sustained OASIS in the previous pregnancy.

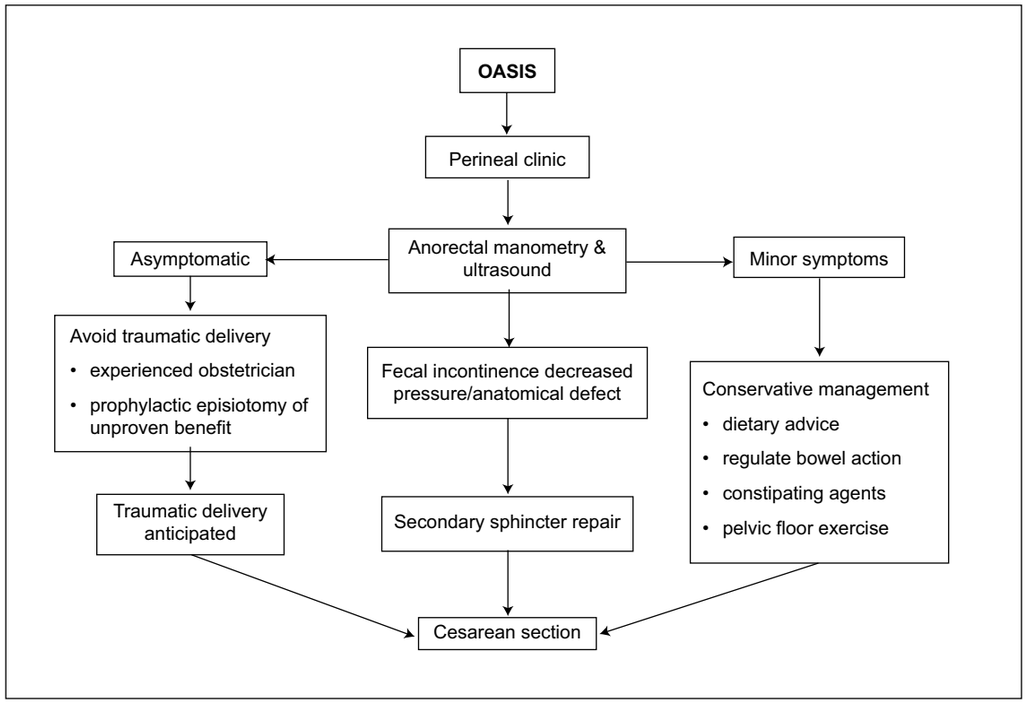

Figure 4 Flow diagram for the management of obstetric anal sphincter injury in subsequent pregnancies

Candidates for cesarean section

Women with mild fecal symptoms should be managed conservatively for their anal incontinence and a prelabor cesarean section advised in an attempt to prevent any further compromise to the sphincter function. Women with anal incontinence should be referred to a colorectal surgeon to consider secondary repair of the sphincter prior to conception and they should be offered a prelabor cesarean section. Fecally incontinent women who wish to consider vaginal delivery can have the secondary repair delayed until they have completed their family.

However, cesarean section is by no means the panacea of obstetrics, and fecal incontinence will not be eliminated, even if all women are delivered abdominally. A mail survey of a cohort of volunteers was conducted in France to estimate obstetric risk factors on fecal incontinence among middle aged women (2640/3000 questionnaires were returned). The prevalence of fecal incontinence was similar in nulliparous, primiparous and multiparous women. Among parous women, this was similar in women with spontaneous vaginal, instrumental or cesarean section deliveries (9.3%, 10% and 6.6%, respectively). Lal *et al.*[16] compared the anal function of 184 women who delivered via cesarean section with 100 women who delivered vaginally 10 months postnatally and found that reported symptoms of anal incontinence were similar between the two groups (5% *vs* 8%, $p > 0.05$).

Candidates for vaginal delivery

As a general rule, OASIS women who are asymptomatic with satisfactory anal pressure measurements and ultrasound imaging should

be counseled that they have a 95% chance of not sustaining recurrent anal sphincter injury or developing new symptoms following a subsequent vaginal delivery.

There is limited evidence regarding the methods that should be employed during labor to minimize recurrence of OASIS during vaginal delivery. The majority of data come from studies on nulliparous women and the results should be extrapolated with caution to women who have previously sustained OASIS.

Antenatal perineal massage

In a randomized study, Shipman *et al.*[17] prospectively studied the effect of perineal self massage with almond oil in 861 nulliparous women 6 weeks prior to delivery and found a 6.1% reduction in second or third degree perineal tears in the study compared to the control group, especially in the over 30 years of age cohort. Similar results were noted by Labrecque and colleagues[18] (who reported a 9.2% decrease in perineal trauma in nulliparous women practising perineal self massage), although this effect did not persist in subsequent vaginal deliveries. By combining the results of the above mentioned studies, Thakar *et al.*[19] calculated that one case of perineal trauma requiring suturing would be avoided for every 13 nulliparous women who performed perineal massage antenatally. The risk of sustaining OASIS was found to be non-significant.

Birthing position

Considerable discussion exists regarding the influence of position during the second stage of labor on perineal trauma. Eason *et al.*[20] reported an increase in the risk of perineal trauma requiring suturing in the upright birth position (using supporting furniture) compared to recumbent positions (weighted risk difference 2%). Retrospective evidence from a study by Gareberg and colleagues[21] described the risk of sustaining a third degree tear as seven times higher in the standing group, and the lateral (side lying) position has been suggested as the most protective posture to the perineum. However, these observations come from small randomized controlled trials, and larger studies are needed before drawing any conclusions and altering clinical practice.

Second stage pushing advice

Fraser and colleagues[22] investigated the effects of early versus delayed pushing by randomizing 1862 women at full dilatation (with epidural *in situ*) to either actively push early or delay pushing unless the urge was too strong or the baby visible. They hypothesized that waiting at least 2 hours before actively pushing would reduce the risk of difficult operative delivery, as measured by cesarean section and midpelvic or low pelvic instrumental delivery rates. Delayed pushing reduced the number of difficult operative deliveries; this was associated with a decrease in cord pH but no difference on third or fourth degree tears was observed.

Use of episiotomy

For years routine episiotomy was encouraged in the belief that it reduced perineal trauma, allowed better healing than tears, and prevented pelvic floor relaxation. In 2000, a Cochrane review[22] showed that routine episiotomy caused more posterior perineal trauma and was associated with more complications compared to selective episiotomy. More recently, Eason *et al.*[20] calculated that avoiding routine episiotomy in five women would prevent one case of perineal trauma requiring suturing with the weighted risk difference in anal sphincter tears being −1% (95% CI −1–0%). An interesting retrospective cohort

study on the influence of episiotomy at first vaginal delivery on the risk of perineal laceration in a subsequent vaginal delivery was published by Alperin and colleagues[24] who identified 6052 women with consecutive vaginal deliveries of live-born term singletons with vertex presentation. Of these, 47.8% had had an episiotomy at first delivery, and the rate of second degree lacerations at the time of second delivery was 51.3% in women with history of episiotomy compared to 26.7% in those without ($p < 0.001$). In addition, third and fourth degree tears occurred in 4.8% of women with previous episiotomy in contrast to 1.7% of controls. These authors extrapolated that for every four women in whom episiotomies were not performed in the first pregnancy, one second degree laceration would be prevented, thus suggesting that the consequences of performing an episiotomy can be perpetuated to subsequent vaginal deliveries presumably because scar tissue has less elasticity.

Use of instruments for operative vaginal delivery

Compelling evidence on the protective effect of vacuum extraction compared to forceps delivery led the Royal College of Obstetricians and Gynaecologists in the UK to recommend that the former should be the instrument of choice for operative vaginal birth. Literature review[25] suggests that one anal sphincter tear is avoided for every 18 women delivered by vacuum extraction instead of forceps (weighted risk difference −6%, 95% CI −8% to −4%).

RISK OF RECURRENCE

The evidence available on this issue is conflicting and appears related to the type of episiotomy practised in the delivery centers. Payne *et al.*[26] (who practised in a center that performed midline episiotomy) prospectively followed 1741 women who had two consecutive vaginal deliveries and reported the recurrence rate to be 10.7% (19 out of 178 cases with a prior sphincter tear, adjusted OR 3.4). The same authors described the occurrence rate of third or fourth degree tears with the first delivery to be 10.2%, an unusually high percentage which was probably attributable to the type of episiotomy conducted.

Peleg and colleagues[27] found 704 sphincter injuries in 4015 primiparous deliveries; in these women, the recurrence rate of severe perineal tear was 2.1% when no episiotomy was performed, 11% with a midline episiotomy and 21% in instrumental deliveries with midline episiotomy. In another retrospective American cohort study[28] of 6068 women, a 7.2% recurrence rate of severe perineal laceration was reported compared to 2.3% in women who had a primary anal sphincter laceration. Statistical analysis of the significant risk factors contributing to the above figures included midline episiotomy (OR 8.5), vertex malpresentation (OR 4.3), shoulder dystocia (OR 2.7) and infant birth weight >3500 g.

It is difficult to extrapolate the above data (from units that perform midline episiotomy) to centers in the UK and Europe where mediolateral episiotomy is routinely practised. Harkin and colleagues[29] reported a series of 20,111 consecutive vaginal deliveries from Dublin in which mediolateral episiotomy was performed, noting that 2.9% of primiparous and 0.8% of multiparous women sustained primary OASIS and that such a severe injury recurred in 4.4% of women. These researchers concluded that although OASIS was increased five fold at next delivery, 95% of women delivering vaginally after previous third and fourth degree tear did not sustain further sphincter damage.

RISK OF ANAL INCONTINENCE

Few studies have tried to establish the risk of anal incontinence in a subsequent vaginal delivery following OASIS. Bek and Laurberg[30] studied 56 women who sustained OASIS and then had subsequent vaginal delivery; 52% of them remained asymptomatic following the second delivery, and only four of 23 women who had transient symptoms after the first delivery reported persistent symptoms after the birth of their second baby. Four women of the original 56 had persistent symptoms of anal incontinence following OASIS and interestingly, three of the four women denied any worsening of their symptoms after the second vaginal birth. Conversely, Poen and colleagues[31] noted that the rate of anal incontinence was 56% in women who had a subsequent vaginal delivery following previous OASIS compared to 34% in those who did not subsequently deliver.

The role of the internal sphincter damage and rectal extension in the development of anal incontinence was highlighted in a study by Sangalli and colleagues[32]. They found that the rate of anal incontinence was 25% following fourth degree tears compared to 11.5% in women who sustained a third degree tear ($p = 0.049$).

Irrespective of the decision that women make for their subsequent delivery, they should be fully aware of the overall risks each mode of delivery entails. For example, cesarean section carries an 11.3% risk of maternal morbidity compared to 4.2% following vaginal delivery[33].

PREDICTIVE FACTORS

Being able to predict the women who would develop anal incontinence following OASIS would prove extremely valuable in counseling and managing patients, but any such evidence from prospective studies is sparse.

Fynes *et al.*[34] followed 59 women who had two consecutive vaginal deliveries at three different time points; 34 weeks' gestation of their first pregnancy and 6–12 weeks postnatally after two consecutive vaginal deliveries. Women with transient fecal incontinence or occult anal-sphincter injury after their first vaginal delivery are at high risk of fecal incontinence after a second vaginal delivery (75% vs. 5% of women with less extensive defects, $p < 0.0001$).

Starck and colleagues[35] carried out an informative longitudinal study, whereby 41 women who suffered a third or fourth degree tear were recruited and followed with anal manometry and endoanal ultrasonography at 1 week, 3 months and 1 year postpartum. The women were asked to complete a questionnaire pertaining to bowel function (Wexner Score) 1 and 4 years after delivery. The most predictive variable of the Wexner score at 4 years was the endoanal sonographic sphincter defect score at 1 week ($r = 0.48$, $p = 0.002$).

AGE-RELATED INCONTINENCE SYMPTOMS

The progression of anal incontinence symptoms over time has recently attracted clinical interest. Fornell and colleagues[36] invited 82 cases and controls (who had participated in a previous prospective study on third degree tears) back to their clinic 10 years after delivery. The patients were asked to complete identical questionnaires on anal incontinence and sexual symptoms to those completed 10 years previously and all underwent anal manometry and endoanal ultrasonography. Incontinence of flatus and liquid stool was more severe in cases than in controls, a finding which was consistent over the years. In women with OASIS, the maximal squeeze pressures were significantly lower at 10 years compared to at 6 months postinjury (as recorded during the initial prospective study). Internal sphincter injury demonstrated by endoanal ultrasonography was associated with significantly more severe incontinence symptoms. Perineal body thickness was similar irrespective of the degree of sphincter tear, but women with perineal bodies <10 mm had more vaginal dryness and

worse flatular incontinence. Of interest was the fact that 10% of the women in the OASIS group had undergone secondary repair of the anal sphincter because of fecal incontinence.

Samarasekera *et al*.[37] investigated the long-term anorectal function and quality of life in three groups of women: group 1 consisted of women who had sustained a third degree tear 10 years prior ($n = 54$); group 2 included the next delivered patient with an uncomplicated vaginal delivery ($n = 71$); and group 3 those who delivered by elective cesarean section ($n = 54$). Women in group 1 had significantly higher rates of anal incontinence and impaired quality of life scores compared to women in groups 2 and 3 ($p < 0.0001$). Similarly, mean resting and squeeze pressures were lower and sphincter defects were more persistent in the study group compared to the two control groups ($p < 0.05$).

Thus, in women who had sustained OASIS, symptoms of anal incontinence as well as quality of life scores may worsen as age and menopause related changes set in.

MEDICOLEGAL PROBLEMS

It is often difficult for a claimant to discharge a burden of proof that a third or fourth degree tear occurred through a lack of skill or care[38]. The usual accusation is that either OASIS was 'missed' or the repair was suboptimal. Up to a third of women having their first vaginal delivery may sustain occult sphincter injury[39], and 'missed' mechanical disruption of the anal sphincter is increasingly recognized as a major contributor to subsequent fecal incontinence.

A consensus statement arising from the conference 'Obstetric anal sphincter injury: Is it time to rethink practice as we enter the Millennium?' held in Birmingham, UK, in 2000 recommended that any woman having had an *instrumental delivery* or *sustaining a perineal tear* should undergo digital rectal examination by an individual trained in the recognition of third degree tears: failure to recognize a significant sphincter injury by not conducting a rectal examination is the principle cause of successful litigation.

A recent meta-analysis indicated that 66% of women remain fully continent of feces and flatus after primary repair and 49% after secondary repair[40]. It follows that the repair of an OASIS must be executed with appropriate skill and care, and the consensus statement further advises that the procedure should be performed by a 'trained professional' in a well equipped and lit operating theater following a set protocol.

In the preconceptional counseling of women who have had previous third or fourth degree perineal tears, risk management and potential litigation become important issues in the group with previous OASIS who elect to have vaginal births. Informed consent is paramount, and it is crucial that all these women are carefully examined by digital rectal examination following delivery and that any repair be conducted according to protocol by experienced trained personnel.

CONCLUSION

Women with previous fecal incontinence who have had successful repair should have prelabor cesarean section. Women with OASIS who are asymptomatic with satisfactory anal pressure measurements and ultrasound imaging should be counseled that they have a 95% chance of not sustaining a recurrence in a subsequent vaginal birth, although anal incontinence may still arise with increasing age. Risk management and potential litigation are important issues in the group with previous OASIS who elect to have vaginal deliveries. Informed consent is paramount and it is crucial that all these women are carefully examined by digital rectal examination following subsequent delivery and that any repair be conducted according to protocol by experienced trained personnel.

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SECTION 4

Phobias

21

Management of tocophobic women

Anna Roland-Price and Zara Chamberlain

INTRODUCTION

Having a baby is usually an exciting time for women, one that is full of joy and happiness. This is not the case for some mothers-to-be, however, as they are encumbered by a morbid dread, and fear, of pregnancy and the birthing process. Although many overcome their anxiety with the help of their partner, family or friends and the support of those caring for them, for others the fear and anxiety remain intense and can best be described as 'a morbid dread of childbirth'. To enter pregnancy with such a degree of apprehension is an obvious detriment to the mother and her unborn child.

Little has been published about why some women fear childbirth, aside from that in Nordic countries and the UK. Sjogren from Sweden followed up 72 women with severe anxiety of childbirth and the support offered to them[1]. Hofberg and Brockington described 26 cases in the UK and cited an 1858 definition by Marce which applied to the women in their study:

> 'If they are primiparous, the expectation of unknown pain preoccupies them beyond all measure, and throws them into a state of inexpressible anxiety. If they are already mothers, they are terrified of the memory of the past and the prospect of the future'[2].

Despite being initially documented in the medical literature over 150 years ago, tocophobia still remains largely unrecognized within the obstetric community as well as the wider health profession. During the past decade, however, interest in fear of childbirth has expanded.

TOCOPHOBIA

The word tocophobia comes from the Greek word tokos, meaning 'childbirth' and phobos, meaning 'fear'. Tocophobia is an intense anxiety or fear of pregnancy and childbirth, with some women avoiding pregnancy and childbirth altogether[3]. Women who suffer from tocophobia often feel alone in their angst. Swedish researchers explored the phenomenon of anxiety and fear in childless women as well as in those with children. Childbirth fear was more frequent amongst primigravidas than multigravidas[3,4]. Tocophobia can be divided into primary and secondary components[4].

Primary tocophobia

Primary tocophobia may have its onset in adolescence, affecting nulliparous women to such a degree that some women never bear a child[2]. This dread has led women to avoid pregnancy for fear of dying, despite their desperately wanting children[2]. Many of these are never able to overcome this fear[2] scrupulously use contraception[2], often using one or more methods simultaneously 'just in case'.

Although a few women remain childless[3], others decide to adopt a child[3]. Occasionally tocophobia is culturally associated, such as

negative feelings towards childbirth which can be passed between mother and daughter[2], a result of sexual abuse[2], or arises after seeing a film depicting childbirth early in life with no support or explanation. Although some women are able to overcome the avoidance of pregnancy, mainly due to a huge desire to become a mother, they still harbor a deep fear[2]. This may result in a decision to terminate the pregnancy[3] or to seek an elective cesarean section as their only alternative[2].

Secondary tocophobia

Secondary tocophobia may be associated with a previous traumatic birth experience[2] such as stillbirth, termination of pregnancy, an obstetric event such as unexplained stillbirth or delivery of a malformed child, or even a normal delivery[3]. Women may also be concerned with pain, their own incapability, possible obstetric injuries, lack of control, lack of partner or familial support and, finally, loss of the baby's, or their own, life[2,3].

SYMPTOMS

Primigravidas and multigravidas display similar symptoms, their fear being so intense that it forces them to request a cesarean section, as labor and vaginal birth are too difficult to contemplate[3]. Behavioral, emotional or physical symptoms[4] may also be present in the form of sleeplessness, crying episodes, restlessness or nervousness. Health professionals should be astute to these manifestations, as they can provide an indication that the woman's underlying distress and anxiety may be greater than it appears.

IMPLICATIONS

Raphael-Leff states that a woman's mental state, particularly her anxiety level during pregnancy and labor, may contribute to complications of labor and the degree of interventions that are required. After delivery, the woman's self assessment of how she has coped is likely to have postnatal psychological repercussions for her, the baby and, in turn, the whole family[5]. Anxiety during the antenatal period has been associated with an increased risk of postnatal depression; bonding and attachment towards the baby can also be affected[6,7]. Additionally, anxiety can lead to an increased number of requests for cesarean and instrumental deliveries[3]. In one Scandinavian study, anxiety and fear were associated with premature birth, post-term delivery, low birth weight and intrauterine growth retardation (IUGR) of the fetus[7].

High levels of anxiety, expressed early or during pregnancy, should alert health professionals to acknowledge the women's distress, react in a supportive manner, and, if necessary, obtain appropriate consultation[7].

PERTINENT LITERATURE REVIEW

Wijma suggests that tocophobia differs from other phobias in that many women's fear of childbirth only increases to a phobic level after they have become pregnant. However, unlike people with different phobias who may be able to have some control over their situation by means of avoidance, the pregnant woman cannot avoid what she fears. She is caught in a situation for 9 months until she is forced to approach the unknown, uncontrollable and unavoidable delivery.

According to a study published in 1981, approximately 6% of pregnant women have an intense, complex and multifaceted fear of childbirth, in which pain is not a dominant factor[10]. A more recent study of 8000 women showed that the rates of intense fear of childbirth affected about 1 in 20 women[6]; of those affected, approximately 50% feared for the baby's health and 40% feared the pain itself[6].

Clearly, how the questions are posed has an effect on the answers given, the literature cites different fears within different reports but what appears to be constant is that intense fear is always present for some women.

In Sweden, fear and a prior bad birth experience represent major reasons for women desiring a cesarean section[11], whereas British obstetricians note that their patients are more likely to ask for a cesarean section on 'maternal request', as opposed to fear of giving birth[9]. When no medical indication is present, debate continues amongst the obstetric community regarding the woman's right to choose how her baby is delivered[9], but very little thought is given to why women choose to have a cesarean section and how to help them to overcome the fear of vaginal birth[9].

A UK cesarean section audit in 2000 found that 7% were for maternal request[3]. However, the exact number of women requesting an elective cesarean section for tocophobia was not known[3]. This is in contrast to Finland and Sweden where fear of childbirth or maternal request represents the reason for about 7–22% of cesarean section births[9].

The findings highlighted above show the importance of antenatal strategies[9] to identify women with intense fear related to childbirth. In Sweden, nearly all obstetric departments have specialized teams to deal with patients exhibiting intense anxiety; these teams include experienced midwives, obstetricians, psychologists, social workers and occasionally a psychiatrist[11]. The value of such efforts underscores the finding of Saisto *et al.*, who found that about half of the women in their study who requested a cesarean section because of anxiety accepted a vaginal delivery after psychological support was offered[9]. One-third who wanted a cesarean section chose not to accept help[9].

Although all women have some degree of anxiety in relation to childbirth, the quality and intensity of the fear is different for women with tocophobia. For many women talking through their fears is helpful, despite the fact that talking through difficult and painful feelings is not an easy thing to do[13]. Under these circumstances, a 'birth reflection' experience can help considerably by allowing the women to think back to a previous birth, clarify events, obtain a greater understanding of what happened, why intervention was necessary and the implications for future births. By allowing women the opportunity to go through their maternity records and discuss their birth experiences, women who felt traumatized (secondary tocophobia) can be identified and, where necessary, offered support. This listening and working through of a previous birth allows the mother (and partner, if present) to verbalize feelings, identify fearful moments and find ways of strengthening her self-confidence.

Women can be informed of the birth reflection service by their general practitioner (GP), midwives based within the hospital and community, physiotherapists and health visitors. Women can also self refer, with women recommending the service to other women. Involvement with family social workers, community mental health teams, psychiatrists and obstetricians can also support women where necessary. For some, this may be the first time they are able to verbalize the trauma they felt and express their views about future childbirth. Others are able to say that although they wanted more children, they felt their previous experience and the fear surrounding it prevented them from doing so. In allowing women further sessions to explore their feelings, many are able to consider further pregnancies. Having a greater understanding of intense fear and anxiety surrounding pregnancy and childbirth can enable health professionals to identify women[13] who are distressed at an initial or early appointment or who immediately request a cesarean section. Such women may have broken down at an antenatal appointment or walked out of a parent education class in tears, unable to stay.

CASE STUDY

A woman presenting with secondary tocophobia was referred by the community midwife to the Birth Reflection Service following the initial appointment. The community midwife recognized her distress and offered her support. The woman sobbed uncontrollably as she remembered the events of her first birth. On reviewing the maternity notes, the delivery appeared to have been a normal straightforward vaginal birth. However, the woman's perspective was one of a traumatic experience where she felt no one had listened to her or involved her in the decision making. She suffered with postnatal depression for 2 years following the birth and was treated with medication.

The second pregnancy was unplanned, and the woman had an appointment to terminate at 9 weeks, but decided, at the last minute, that she could not go through with it. She felt caught, because she also felt she could not go through labor again. As a result, she was late in seeking antenatal care (18 weeks).

At the initial meeting, she was able to begin to share her feelings with the midwife counselor. She hated the thought of an 'alien' being inside her, the feeling of 'it' moving around inside of her, and felt sickened when anyone acknowledged her bump. Although support was provided it was not until the 36th week of pregnancy that she dared think about 'the alien' as her baby. Only then did she allow herself to walk past baby items and purchase something for the baby.

Sharing and acknowledging her feelings was not an easy process and involved much emotion and pain as she recalled the last birth. She was petrified of her forthcoming birth and felt that the professionals had not taken her seriously.

In preparation for the birth, meetings were arranged once a month, gradually increasing to fortnightly and then weekly from approximately 36 weeks. When these appointments were made, it was understood by the midwife counselor that if the woman felt content and able to cope, then she could cancel an appointment if she so wished, thus allowing the woman to feel more in control and giving her flexibility and trust. Meetings included visits to the labor ward and obstetric theaters, and introducing the woman (and partner, if present) to members of staff. As part of the management, an early epidural was discussed which enabled the woman to feel more in control.

On admission, an epidural was administered at 4 cm dilation. The woman labored well and achieved a spontaneous vaginal birth. On later reflection of her birth, her experience was completely different to her first one, as she felt that people had listened to her and included her in the decision making.

AN EXAMPLE OF SOME PRIMARY TOCOPHOBIA EXPERIENCES

Although there are similarities between primary and secondary tocophobia, distinct differences also exist. In our experience, primigravidas had not shared their fear with anyone, even when breaking down at the midwife or general practitioner's (GP) appointment. It was only when pressure from a partner to start a family was applied that they were able to confide that they had a fear of childbirth, and in some cases this did not happen until well into the pregnancy. The common factor that they all shared was that in the process of giving birth and in dilating during the second stage to deliver the baby, they thought that they would die. They were unable to disclose this fear other than to ask for a cesarean section simply saying they had a fear of childbirth.

Because this fear is profound and terrifying women find it difficult to express and share their true feelings or seek preconception advice. When sharing their intense anxiety (they did not share their real fear) with a health professional, these women were often told 'this is normal, all women are afraid'. The

fear, however, was so dominant that they knew this was not the case and often felt undervalued, unable to share their real fear of dying. It was not so much about the pain of childbirth but more about the dilating during the second stage being described, as like trying to get 'something the size of a melon through an opening the size of a small orange'. They felt that in the process they would die.

Many women knew that their fear was not rational, but were unable to feel differently. They felt that a cesarean section was their only option. This fear was so great that they also appeared to be in denial of their pregnancy. In meeting with these women over a number of years, although few in numbers, they all presented with a similar history, disclosing that they had this fear for as long as they could remember and, while they really wanted a baby, they delayed starting a family for as long as possible. Eventually with pressure from their partner, they agreed to have a baby and, while they stopped contraception, they did not plan for it to happen either. Whereas their partners were overjoyed by the pregnancy, the women were struck by fear and in denial, seeking care late and wearing clothes that concealed the pregnancy. They often avoided antenatal classes or only attended some of them. They also disclosed, in the attempt not to confront their pregnancy, that they were often unable to enter baby shops to look at baby equipment or clothes, and often were unable to buy any of the items required to create a nursery. Frequently it was the partner who did this and in some instances the women did not allow anything into the house that could remind them of the pregnancy. They disliked discussing the pregnancy with friends or relatives. There was also a reluctance to share their fears with medical professionals as their perception was one of being judged for not wanting the baby, which was not the case; the baby was very much wanted.

These women's thoughts were very positive regarding the baby and there was a feeling of great excitement in thinking about the baby once born. However, there was a strong sense of wanting to fast forward the whole process and to be able to hold and nurture their baby. By attending regular sessions to explore their fear they were able to share something that was so profound to them, this fear and dread of death. They understood that their fear was not logical and sharing it was profound, as they felt they would be judged as being 'mad'.

Regular sessions with these women helped build the trust between the midwife counselor and the women who were able to learn how their bodies responded and to gain a greater understanding of the labor process. The midwife counselor, with the permission of the women, shared with the staff the women's fear of dying during labor. In doing this, it raised the staff's awareness of tocophobia and while most staff were keen to learn and be supportive, there were staff who felt that all women have anxieties about birth and that this was no different. This included some doctors as well as midwives. Although these members of staff were in the minority, one cannot ignore the fact.

Over the weeks, women started to explore the idea of a vaginal birth as opposed to a cesarean section and as the due date approached, the midwife counselor discussed with the women the possibility of a vaginal birth. These women often stated that they really wanted a vaginal birth but that a cesarean section was the option for them to get through their specific fear.

The next step was to prepare a robust care plan with the women. With their agreement, details pertaining to their fears, issues and needs were documented in the case notes and within their care plans. One of their wishes was often that they could 'bale out' at any time and have a cesarean section. Although they wished to have a vaginal birth, they had a deep-rooted need to feel that they could have a cesarean section. This gave them a sense of control. As only a consultant can agree a cesarean section,

an appointment was made with a consultant, including the midwife counselor, where all three could discuss this issue. Most consultants agreed to write in the woman's labor notes that she could have a cesarean section at any time in her labor should she request it and the note also stated clearly that the woman suffered from tocophobia. This 'safety net' is often not used. It cannot be over emphasized how important this was to these women; however, it was also explained that on a busy labor ward a cesarean section could not always be performed to order. The women understood that if there was an obstetric emergency that it would take priority and they would have to wait. This was also the case regarding an epidural and women accepted this.

Whilst one-to-one care is highly recommended, carers must not promise women support that cannot be delivered. Honesty and trust is very important in the relationship between members of the multidisciplinary team caring for these women.

The midwife counselor should meet all the obstetric registrars who will be working on the labor ward and should explore the individual woman's birth plan with them, explaining the extent of the fear. For many, this may be the first time they have heard of tocophobia, so educating and sharing is paramount. It is hoped that in meeting with the registrars, the registrars will have a greater understanding if the woman feels the need to request a cesarean section in her labor that the consultant has agreed can be performed.

These women, often remaining in denial regarding their pregnancy, would remain in denial when they went into labor and would avoid the hospital and remain at home for as long as possible, often coming into hospital well into established labor. With the support of the multidisciplinary team, women with the phenomenon of fear of death at the time of cervical dilation achieved a vaginal birth. Aided by the therapeutic process, these women were able to share this deep-rooted fear, despite feeling at the beginning of their pregnancy that the only option for them was a cesarean section.

There was also a high level of commitment by the midwife counselor to constantly ensure that communication was effective and the support was constant. Every possibility was meticulously covered to ensure that they received the one-to-one care and support they felt they needed to achieve a vaginal birth. Obviously this approach is labor intensive and throws into question the realism of the commitment with larger numbers of women in busy labor wards. However, with the right support these women were able achieve a vaginal birth and confront their fear. One could argue therefore that this kind of involvement is indeed cost-effective. Psychologically and emotionally the women feel listened to and supported, which may have long-term effects for the individual woman and her family.

Not all consultants agreed to documenting that a cesarean section could be carried out at anytime during labor, with what was perceived to be no medical indication. If this was the case for those women, they felt that their only option was to have an elective cesarean section on 'maternal request'. In our experience, none of the women who had the cesarean section option documented in their notes needed to use the option.

In our practice, over a period of time, women with tocophobia have returned to have a second baby and been able to have a vaginal birth; they no longer needed the previously required support. Having had a vaginal delivery the first time, seemed to have confronted their fear and enabled them to enjoy a next pregnancy. During their second pregnancies these women embraced all aspects of maternity care and advice which placed them in a healthier position.

SUMMARY OF THE MANAGEMENT OF WOMEN WITH TOCOPHOBIA

Health professionals need to be able to recognize what may be classic symptoms of

tocophobia in women such as vague distress unrelated to anything specific, excessive nervousness or anxiety, bouts of crying, odd behavior and early requests for cesarean section. Such women should be brought into contact with a health professional(s) who can give expert advice where possible and create an atmosphere where the women can feel safe to disclose their fear(s), where they can feel heard and listened to without feeling judged. The building of a trusting relationship involves the midwifery team, the obstetric team and psychological support. These women need practical help rather than 'labeling'. Although some women feel relief that tocophobia is acknowledged and they are not alone in their fear, for some the 'label' may be reassuring. Health care workers need to realize that working closely as a team is imperative for these women, to ensure that the appropriate professional is available for advice and support.

It is important to develop a plan of care that documents information provided to help support the team caring for these women, including the extent of the women's fear and, ensuring that the women are part of the decision-making process. Women may wish to have a vaginal birth, but may have been sexually abused as a child and want minimal vaginal examinations, or only female attendants; these requests can be built into the birth plan. In the authors' experience, the more women are able to share with the professionals caring for them, the happier they are with the birth experience. One-to-one care is also important for these women, as is an early epidural which provides more control from a psychological perspective.

Taking the women to the labor room and obstetric theater for an explanatory tour can help dispel any preconceived ideas about how they imagine the rooms to be, especially for the nullipara or for the multipara who has previously delivered at another institution. Introductions to members of staff who may be on duty can also be helpful. For some women, the fear is so intense that it may take several visits to the hospital before they feel secure and safe enough to enter the labor ward. As trying as this may be for some health professionals, the multiple visits can be a powerful experience for some women that allows emotions and fears to be worked through as well as clarifying any distorted notions of what the room might contain. This is especially true for the primigravida, whereas for the multigravida, it may be about lost expectations, or dreams of how they imagined the birth.

SUPPORTING WOMEN

It is important that women with fear of childbirth have access to professionals who are qualified to support them. The NICE guidelines regarding counseling women in relation to cesarean section state that women who have a fear of childbirth should be offered counseling to help them address their fear in a supportive manner[14]. Counseling support is an effective way to help women experience birth in a way they find acceptable[11].

Midwives occasionally undertake counseling roles beyond their training and abilities[9]. It is necessary for midwives and health professionals to work within their remit and not press for information that may open painful past experiences, for example those in childhood that may not be able to be fully worked through such as sexual abuse. Health professionals need to be aware of boundaries. Respect for the women at this vulnerable time is paramount.

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SECTION 5

Medication issues

22

Routine vitamin, mineral and micronutrient supplementation

Louis G. Keith, Tawanda Ngorima, Kantha Shelke and Mahantesh Karoshi

INTRODUCTION

Little doubt exists in the minds of the medical profession and much of the public that the connection between maternal nutrition and fetal outcome is important. There is, however, much confusion about the most efficient method to achieve an adequate nutritional status at the start of pregnancy, especially if a nutritional deficiency is present. No consensus regarding the definition and/or understanding of 'adequate nutrition' exists, and even less uniformity of opinion is present for a definition of 'optimal nutrition', even though some authorities might suggest that diet alone supports health and longevity. The components of diet are inexorably tied to culture.

Beginning with birth, each of us eats foods which are usually chosen by individuals who have had no formal training in domestic sciences, dietary technology, or food preparation. Mothers and grandmothers sanctioned food choices determined by local availability, budget, accessibility of refrigeration and community or religious practices that often stretch back to antiquity. The nutritional value of these diets is highly variable.

Under such circumstances, when healthcare professionals speak with clients in developed nations, their words may provoke head-shaking to signify some degree of understanding, but it is highly likely that patients differ in their understanding of adequate nutrition. This scenario is only part of the problem. In the authors' opinions, a far greater problem exists in that the science of nutrition is relatively young in the spectra of medical disciplines and often gets short shrift in the educational process. Despite a vast body of research into specific dietary problems, much of the available literature is confusing because of lack of standardization of methodologies of study, indecision about whether specific nutrients should be evaluated alone or in combination, and absence of agreement as to whether the dose should be tested in relation to what a normal person might consume in a 24-hour period or as a megadose that exceeds anything that can be found in a supposedly normal diet.

The same may be said regarding optimal vitamin supplementation in pregnancy, be it the type or the dose. Table 1 has been prepared to provide health care professionals a handy guide that they can share with their patients. Not only are the nutrients and their respective doses listed, but also cited are the appropriate sources of the information. It is hoped that practitioners will feel free to copy this table, from either the printed or electronic version, and share it with patients and their families. A careful perusal of recommended dosages reveals a lack of consistency even among those agencies that deal with these issues on a daily basis. Where more than one source may be considered authoritative, both are listed.

Table 1 Recommended nutrient intakes, deficiency effect on expectant mother and offspring, authority source and effect of excess

Nutrient	*Recommended intake for pregnant women*	*Deficiency effect on expectant mother*	*Deficiency effect on offspring*	*Source*	*Effect of excess*
Fiber	28 g	Constipation	None known	National Academy of Sciences[1]	Malnutrition and depletion of vitamins
Folate	600 µg per day DFE*	Folate-deficiency anemia: tiredness, breathlessness, palpitations, depression	Neural tube defects	*Food and Nutrition Board[2]	Toxicity from folate is low because it is water soluble and is regularly removed from the body through urine
Iodine	220 µg* 150 µg**	May be accompanied by catastrophic consequences, including spontaneous abortion, stillbirth and increased perinatal mortality	Newborns: may exhibit goiter, mental retardation and cretinism, the most extreme form of neurological damage from hypothyroidism	*Food and Nutrition Board[3] **American Thyroid Association[4,5] † National Institutes of Health[6]	†Thyroid dysfunction and skin irritation
Iron	27 mg/day* 30 mg/day**	Anemia	Premature delivery, low birth weight	*Food and Nutrition Board[3]* *Centers for Disease Control[7]	Gastrointestinal distress
Omega 3 - DHA/EPA	1200 mg* 1400 mg**	Fatigue, poor memory, dry skin, heart problems, mood swings or depression and poor circulation	Adverse effects on visual and neurological development	*The DHA/ Omega-3 Institute[8] **Food and Nutrition Board[9]	None known
Omega 3 - DHA	200 mg/day* 300 mg/day**	Fatigue, poor memory, dry skin, heart problems, mood swings or depression and poor circulation	Adverse effects on visual and neurological development	*World Association of Perinatal Medicine, the Early Nutrition Academy and the Child Health Foundation[10] **National Institute of Health and the International Society for the Study of Fatty Acids (NIH/ ISSFAL)[11,12]	None known

continued

Table 1 *Continued*

Nutrient	*Recommended intake for pregnant women*	*Deficiency effect on expectant mother*	*Deficiency effect on offspring*	*Source*	*Effect of excess*
Selenium	60 µg	Pre-eclampsia, first-trimester miscarriages and recurrent miscarriages	Weakens the immune system; severe deficiency associated with Keshan disease, Kashin-Beck disease and myxedematous endemic cretinism	Food and Nutrition Board[13]	Selenosis: fatigue, gastrointestinal upset (nausea, vomiting, stomach pain, diarrhea, garlic breath, metallic taste in the mouth), hair and nail loss or blotchy nail beds and mild nerve damage
Vitamin A	750–770 µg RAE (retinol activity equivalent)	Night blindness, xerophthalmia	Impaired immunity, impaired vision	Vitamins, Food and Nutrition Board[14]	Birth defects
Vitamin B3 (niacin)	18 mg/day for pregnant and breastfeeding women* 30 mg/day for women under 18 and 35 mg/ day for women over 18**	Hyperemesis gravidarum, pellagra	No human studies	*Food and Nutrition Board[15] **WebMD[16] †Drugs.com[17]	Nausea, vomiting, severe sensory neuropathy Assigned pregnancy category C by the FDA when given in doses above the RDA†
Vitamin B6 (pyridoxal phosphate, pyridoxamine phosphate)	1.9 mg/day	Overt symptoms are rare	May result in lower APGAR scores	Food and Nutrition Board[2]	None known
Vitamin B12	2.6 µg†	Pernicious anemia	Irritability, failure to thrive including falling off in growth rate, apathy, anorexia, developmental regression, limited hepatic reserves, refusal of solid foods, megaloblastic anemia* †Increased risk of neural tube defects	*Dror and Allen[18] **†National Institutes of Health[19] †Centers for Disease Control and Prevention[20]	**None known
Vitamin D	4000 IU*	Increased risk of cesarean delivery, muscle weakness, poor muscle performance*	Rickets	Centers for Disease Control and Prevention[21] *WebMD[22]	*No evidence of toxicity

continued

Table 1 *Continued*

Nutrient	*Recommended intake for pregnant women*	*Deficiency effect on expectant mother*	*Deficiency effect on offspring*	*Source*	*Effect of excess*
Zinc	40 mg for women >19 years, 34 mg for women 14–18 years*	Impaired growth and development, preterm deliveries, pre-eclampsia, hemorrhage, infections and prolonged labor	Congenital anomalies	*National Institutes of Health[23]	*Ingestion of 2 g of or more can cause nausea, vomiting and fever

DFE, dietary folate equivalent; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid

Even as recently as 10 years ago, it might have been deemed superfluous to discuss vitamins, minerals and micronutrients in a monograph devoted to preconception counseling. This is not the case for three important reasons.

First, people are beginning to recognize that previously prepared foods, stored at a low temperature and then reheated or maintained at a constant warm temperature for hours before consumption, may lose a significant, albeit unknown, portion of their expected values compared to what would have been present had they been eaten immediately or shortly after cooking. Such food is found in cafeterias, steam lines, hotel buffets, etc. This problem exists totally apart from other issues related to 'fast foods' that are eaten shortly after their preparation. Other problems that affect food nutrient content include the use of artificial light and hormones during the growing period, the need to pick fruits and vegetables in a preripened state for transport to the point of sale, and the addition of chemicals or processes that prolong shelf life.

The second reason relates to a continually increasing awareness that dietary inadequacy that exists before pregnancy cannot immediately be rectified once pregnancy commences. A prime but not exclusive example is the relationship between serum folate levels and neural tube defects. Much of the existing literature fails to stress that it is ineffective and perhaps disingenuous to exhort patients to take folic acid only when they are pregnant, because 50% of pregnancies are unintended and any folic acid taken after the 28th day following conception does not affect the neural tube which is already formed by that time. Recent publications and governmental advice center on the need to provide entire populations with adequate folate supplementation before pregnancy because (1) patients are not routinely tested for folate levels, meaning that those who are deficient are unknown, and (2) many patients, especially those in their second pregnancy or higher, tend to come for their first prenatal visit some time after the 28th day following conception because they believe they know the 'routine' or, in the case of grandmultiparas, are burdened with childcare responsibilities. Moreover, physicians now recognize that folic acid is of benefit throughout the remainder of a pregnancy because of cellular development and synergy with B vitamins.

Third, it is clear that governmental decisions to fortify specific foods are not sufficient to eliminate all problems. Here again, folate is a prime example. In 1992, the United States Public Health Service issued a recommendation that all women of childbearing age consume 400μg of folic acid on a daily basis for the prevention of neural tube defects. Six years later, the Institute of Medicine offered

similar advice. Women were informed they could obtain adequate amounts of folate by taking a folic acid supplement, taking a multivitamin containing the requisite amount of folic acid among other constituents, or eating cereal grain products fortified by 100% of the RDA (recommended daily allowance) of folic acid. In 1998, the US Food and Drug Administration required mandatory fortification of cereal grains with 140μg of folic acid per 100 g of cereal grain product, including those grain products that were imported, such as Italian pastas. This enormous effort resulted in a 27% reduction in the incidence of neural tube defects in 1999–2000 compared to 1995–1996[24]. The decline in incidence continues, but it has not been total, perhaps because the fortification process was confined to wheat grains and a large percentage of the American Hispanic population consistently eat products made from corn meal, something not considered at the time of publication of the original fortification guidelines. Not fortifying corn products may not be the entire reason for the smaller response in the American Hispanic population, but it is significant that the largest manufacturer of corn tortillas in Mexico has voluntarily added folate fortification (Linda Van Horn, personal communication, July 20, 2009). The information cited here contrasts with the public health considerations relating to food fortification and/or comprehensive multivitamin products for pregnant women that provide the internationally recommended levels of folic acid rather than relying on obtaining folate and other essential vitamins, minerals and micronutrients in dietary choices.

CRUCIAL ISSUES FOR HEALTH-CARE PRACTITIONERS

Although health-care practitioners generally are familiar with the reputed value of adequate maternal nutrition in terms of its effect on pregnancy outcomes, often they are less familiar with the value of supplementation during pregnancy. Any meaningful discussion of supplementation must address three crucial issues – who to supplement, how to supplement and what to supplement.

Who to supplement

Once again, the profession is confronted by a dichotomy. Much of the literature strongly recommends that only those with known deficiencies receive supplements. This would be reasonable if it were possible to test for all essential pregnancy-related vitamins, minerals and micronutrients in a cost effective and universally applied manner. Such testing routinely is not available in most hospitals where the majority of deliveries are conducted. Even if it were, the unpredictability of pregnancy means that testing could not be carried out in a rational and/or cost effective manner.

Faced with these limitations, routinely supplementing women of childbearing age is a rational means of ensuring that women have adequate levels of essential vitamins, minerals and micronutrients when they become pregnant. In the long run, such therapy is capable of circumventing the dietary variations that exist within populations and between individuals, each of whom may be convinced that her particular diet is adequate, if for no other reason than it may be prepared by someone outside her home and/or at great expense. Of great importance, supplementing that is begun before pregnancy can be continued during the pregnancy by changing to a traditional prenatal vitamin, continuing into lactation and the time before the next conception.

How to supplement

There is no simple explanation regarding this issue, because neither the medical profession nor pharmaceutical manufacturing associations have determined whether it is more

advantageous to supplement with single or multiple components in a given pill. Either is possible, and in the early days of supplementation practice, it was common to prescribe separate tablets for iron and for vitamin supplementation. Knowledge of the essential pregnancy-related requirements for specific vitamin constituents has increased exponentially since 1990, and many clinicians have begun to see the value of prescribing a 'balanced palate' of components that includes vitamins, minerals and micronutrients in one pill or capsule. Thus, the concept of 'monotherapy' has evolved, although admittedly monotherapy is reasonable if one holds to the concept that supplements should be advised only when specific deficiencies are present. In the authors' opinions, however, this line of thinking fails to protect the public health in terms of pregnancy well-being because, with rare exceptions, clinicians are unaware of the relative states of deficiency or adequacy of circulating levels of vitamins, minerals and micronutrients in their patients. Moreover, clinics and hospitals that are very proficient in conducting obstetric deliveries are not at all equipped to accurately analyze blood samples for circulating levels of important vitamins, minerals and micronutrients.

What to supplement

Given the circumstances cited above, all women of childbearing age who engage in sexual relations could become pregnant and should be advised to take a vitamin supplement that contains folate in the requisite dose, along with vitamin B12. In this regard, it is noteworthy that as of early 2009 one of the major worldwide producers of birth control pills is adding folic acid fortification to each pill. We believe it is not practical to assume a good diet will provide everything needed for a healthy pregnancy, because (1) there is no agreement on what constitutes a good diet for everyone, (2) evidence suggests that significant numbers of the literate public do not follow the written guidelines and recommendations concerning healthy eating as they relate to pregnancies, and (3) such advice is without meaning for those segments of the population that are marginalized, living below the poverty level, and who seek prenatal care late in pregnancy. Folate is not the only vitamin that may be deficient in the general population, as shown by a recent national dietary survey in the United States that sampled women aged 19–49 and showed that 90% had daily iron intake that was below the reference nutrient intake (RNI)[25].

We agree with other authors[26,27] that it is necessary to anticipate the increased need for micronutrients, because the only rational way to ensure that these essential elements are present during the critical times of pregnancy is to provide them before pregnancy. This simple concept can and should be part of the counseling provided to every women of reproductive age when she has a medical encounter for whatever reason.

DEFINITIONS

Dietary reference intakes were developed by the Institute of Medicine. The acronym 'DRI' generally characterizes a set of reference values used for planning and assessing nutrient intake for healthy people. Three important types of reference values in the DRI include recommended dietary allowances (RDA), adequate intakes (AI) and tolerable upper intake levels (TUIL) (often shortened to UL). The RDA recommends an average daily dietary intake level sufficient to meet the nutrient requirements of nearly all (97–98%) healthy individuals in each age group and sex. An AI is set when there are insufficient scientific data available to establish an RDA. Commonly, AI meet or exceed the amount needed to maintain a nutritional state of adequacy in nearly all members of a specific age group and sex. On the other hand, the UL is the maximum daily intake unlikely to result in adverse health effects.

PROBLEMS IN THE LITERATURE

The accumulated literature on vitamins, minerals and micronutrients is impressive, to say the least. Terms that describe the quantity and variety of research and opinions might include 'staggering' or 'daunting', and therein lies the problem. The average practitioner has little time or inclination to read even a small quantity of what is available and thus may turn to reviews and committee opinions for clinical guidance. Even these are not in agreement, as evidenced by the heterogeneity of information in reviews that are judged as authoritative, such as the Cochrane database.

The recitation of each controversy surrounding the vitamins, minerals and micronutrients mentioned below will add nothing to the clinical acumen of any health-care professional who may read this chapter. On the other hand, we believe it useful to mention our biases at this time. Simply stated, we believe that modern diets can be deficient in vitamins, minerals and micronutrients for several reasons – overproduction in some farming areas, the use of chemical fertilizers, the need to harvest unripe produce and allow ripening under controlled environmental conditions, and the need to pack foodstuffs in CO_2 for transport, etc., among others. We also believe that supplementation should be started before conception in young women who may or may not be contemplating pregnancy. Finally, we believe that supplementation should be continued after pregnancy throughout lactation and into the interconceptional period, so supplementation becomes a way of life based on the recognition of the inherent deficiency of modern diets in most individuals.

STRATEGIES TO IMPROVE NUTRITION

Recent concerns about dietary inadequacy have led to various strategies to improve nutrition; these range from changing dietary components to reducing social isolation as a means of encouraging better food intake. Each is discussed below.

Functional foods

Functional foods are provided to confer a 'benefit' to the diet beyond that of simple nutrition. In this regard, the nutritive value of common foods can be enhanced by several means, including but not limited to probiotics, prebiotics, synbiotics, omega-3 fatty acids and fibers. The catch-all term for this type of additives is nutraceutical, which can also be used to denote vitamin supplements.

Fibers

Fibers are either readily fermentable by colonic bacteria or only slowly fermentable. They act in several manners, not least of which is exerting a 'mop and sponge effect' in the colon and assisting in the formation of the fecal contents.

Nutraceutical

Dr Stephen DeFelice coined the term 'nutraceutical' in the 1990s and defined it as 'any substance that is a food or a part of a food and provides medical or health benefits, including the prevention and treatment of disease'[28]. Such products may range from isolated nutrients, dietary supplements and specific diets to genetically engineered designer foods, herbal products and processed foods such as cereals, soups and beverages. It is important to note that this definition applies to all categories of food and parts of food, ranging from dietary supplements such as folic acid, used for the prevention of spina bifida, to chicken soup, taken to lessen the discomfort of the common cold. This definition also includes a

bioengineered designer vegetable food, rich in antioxidant ingredients, and a stimulant functional food or 'pharmafood' and fibers.

Prebiotics

Prebiotics are 'non-digestible food ingredients' that selectively stimulate a limited number of bacteria in the colon to improve the health of the host. Present-day prebiotic research is concerned with enhancing probiotic flora.

Probiotics

A probiotic is defined as a 'live microbial food supplement' that beneficially affects the host by improving its intestinal balance. Lactic acid bacteria, particularly *Lactobacillus* spp. and *Bifidobacterium* spp., are the best-studied probiotics at the time of this writing and can be combined with food products such as cereals, bioyogurts and drinks for benefit of gastrointestinal (diarrheal and irritable bowel syndrome) and non-gastrointestinal conditions (candidiasis and urinary and respiratory tract infections).

Synbiotics

These substances contain complementary probiotic and prebiotic ingredients that interact synergistically toward maintenance of a desirable microbial population in the intestine.

The Mediterranean diet

Simply stated, this diet contains high quantities of vegetables, legumes, fruits and cereals (largely unrefined); a moderate-to-high intake of fish; a low intake of saturated fats in contrast to a high intake of unsaturated fats, especially olive oil; a low-to-moderate intake of dairy products, mostly in the form of cheese and yogurt; a low intake of meat; and a modest intake of alcohol mostly in the form of wine. This diet is widely viewed as promoting healthier aging, increasing longevity, and possibly reducing the risk of developing Alzheimer's disease later in life.

Reducing social isolation

Regardless of age, dining with other individuals has many advantages compared to dining alone. Granted that many women of reproductive age are single and often employed, special efforts must be made as part of the counseling process when pregnancy is desired to inform patients that reliance on modern fast foods is not a means to enhance nutrition and that eating with co-workers and/or family has numerous intangible benefits. Most research in this area has been confined to older individuals, many of whom were residing in institutional facilities. Be this as it may, there is no reason to believe that the positive effects of communal consumption that have been observed in older individuals would not pertain to the young, regardless of whether they are pregnant[29].

'ESSENTIAL MATERNAL/ FETAL BUILDING BLOCKS

Folate

- General – folic acid (pteroglutamic acid or PGA) is a synthetic form of folate. Naturally occurring folate is abundant in dark green leafy vegetables, orange juice, legumes (beans), nuts, asparagus and other select foods. Meat, with the exception of liver, is not a good source of folate. Folic acid, as contained in commercial products or fortified foods, is generally more bioavailable than when consumed from

food alone. Indeed, it has been suggested that without supplementation, one would need to ingest enormous quantities of green leafy vegetables to even approximate daily requirements. It also has been suggested that the actual content of folate in foods known to contain high amounts has been declining on an annual basis for some years because of overproduction and the use of artificial fertilizers.

- DRI – folate requirements increase during pregnancy, a fact that has been appreciated for decades. What has not been appreciated until recently is that folate deficiencies must be addressed before the woman becomes pregnant, because many women do not receive medical care until after the 28th day of conception, at which time deficiency cannot be corrected in time to prevent neural tube defects [which] may have already occurred.
- The RDA for folate during pregnancy, as established by the Institute of Medicine in 1998, is 600 μg per day DFE [dietary folate equivalent], this being approximately 50% higher than that of non-pregnant women. Prenatal vitamin supplements contain from 400 to 1000 μg of folic acid. The higher doses are in excess of the 600 μg per day folate DFE for pregnant women.

Deficiency

- Neural tube defects (NTD) occur more frequently in the presence of folate deficiency. The most common include anencephaly and spina bifida, which result from failure of closure of the developing neural tube as it overlies the developing embryonic brain and spinal cord, respectively. This closure occurs by the 28th day of embryogenesis (42 days after the onset of the last menstrual period). Approximately 3000 NTD-affected pregnancies occur on an annual basis in the US alone[1], and the worldwide numbers may still be as high as 300,000 per year, although the incidence ranges widely (0.8 per 1000 births in certain areas of the US to 13.8 per 1000 births in north central China)[26,27].
- Cardiac defects – folic acid containing supplements consumed early in pregnancy have been associated with reduced risks for offspring with heart defects, especially ventricular septal defects and conotruncal defects (e.g. tetralogy of Fallot and transposition of the great arteries)[30]. Although controlled intervention trials are lacking, secondary analysis of a Hungarian randomized controlled trial (RCT)[31] showed reduced occurrence of both cardiovascular anomalies (OR = 0.42) and urinary tract anomalies. Studies in other jurisdictions have reported similar decreases.
- Other positive associations have been reported, including reductions in the incidences of colorectal cancer, breast cancer and possibly vascular disease[26,27]. Of perhaps greater interest to obstetricians/gynecologists is the report that preconceptional folic acid supplementation [for] 1 year or longer was associated with a 50–70% decrease in the risk of early spontaneous preterm delivery between 20 and 28 weeks, a finding that remained after adjustment for maternal age, race, BMI [body mass index], education, marital status, smoking, parity and history of preterm birth[32].

Supplementation

- In 1992, the US Public Health Service recommended that all women of childbearing age consume 400 μg/day of folic acid from supplements, fortified foods, or both, in addition to consuming a varied diet to reduce the likelihood of their having an NTD-affected pregnancy[33]. The Institute of Medicine followed in 1998, advising that all women capable of becoming pregnant consume this important vitamin[2]. Other countries have agreed, with some including the recommendation that supplementation begin in the preconceptional period. This change is considered of great importance because numerous investigations worldwide document that policies advocating supplementation beginning in pregnancy alone are not sufficient to produce the desired reduction in NTD prevalence.
- The 400 μg dose is the amount observed to be associated with NTD risk reduction in most epidemiological studies, supporting the conclusion that periconceptional folic acid use significantly reduces the [incidence] of NTD. It is also the dose [used] in the large scale Chinese intervention trial (N = 250,000)[26,27].
- The 400 μg dose is accepted worldwide even though the only genuine occurrence RCT (NTD in the absence of prior-affected offspring) used a dose of 800 μg folic acid. In this study, the frequency of NTD was zero among 2471 women receiving 0.8 mg, compared to six among 2391 not so receiving[34], in which the expected NTD cases were 6.9 and 6.7, respectively. This study used 800 μg of folic acid, not because the authors had any scientific evidence of its superiority, but because this dose was provided gratis to the investigators. In the Chinese study mentioned above, 400 μg of folic acid was used selectively in specific geographic regions and reduced NTD occurrence by 79% in high incidence regions (0.65% background NTD incidence) and 41% in low incidence regions (0.08% background NTD incidence)[35].
- Although the 400 μg/day is a reasonable dose of folic acid for reducing NTD in the general population, it is considered insufficient for women who have previously had an infant with an NTD. Here the recommended dose is 4 mg per day[36] (ten times the normal), based on a Medical Research Council trial that resulted in a 72% reduction in NTD recurrence[37].

Fortification

- Folic acid fortification programs (i.e. adding folic acid to food) are justified because most women of reproductive age still do not take folic acid supplements (especially before becoming pregnant) and because educational efforts pertaining to NTD risk reduction have not been completely effective in modifying behavior related to supplement use. By 2007, 54 countries had regulations regarding mandatory wheat flour fortification[38]. In the US, as noted above, folic acid also is added in specified amounts to all cereal grain products (bread and pasta, for example) that then are labeled "enriched". Even so, it is estimated that, of US women of reproductive age, only 8% consume equal to or greater than 400 μg/day[39], thus supporting the conclusion that most US women need to take a folic acid supplement to achieve the US Public Health Service/Institute of Medicine (USPHS/IOM) recommendation of 400 μg/day.
- Racial and ethnic disparities exist, with Hispanic women having the highest rate of NTD and the lowest use of folic acid supplements[40,41]. To what extent this disparity exists because of the propensity of Hispanic women to preferentially consume products containing corn flour on a daily basis as would occur with tortilla consumption is unknown. It is a reasonable conjecture, although it also is reasonable to presume that other factors may be working concomitantly.
- The incidence of NTD was inversely associated with folate status in a large Irish cohort study in which the lowest prevalence of NTD was associated with a mean serum folate of ≥7 ng/dl and a mean serum red blood cell (RBC) folate concentration of approximately 400 ng/ml[42].
- Effect of excess – the Institute of Medicine[43] found no substantiated evidence of toxic effects, although other potential adverse effects are: (1) potential interference with the diagnosis of vitamin B12 deficiency-based neurological disease (masking); and (2) potential increase in numbers of twins, a finding ultimately thought to be related to confounding by a high preponderance of fertility interventions.

Iodine

- General – iodine is an essential element that is required for the synthesis of the thyroid hormones of thyroxine (T4) and tri-iodothyronine (T3) that play pivotal roles in metabolism. Deficiency (hypothyroidism) and excess (hyperthyroidism) are well known to medical practitioners throughout the world. Iodine in the form of iodate commonly is used as an additive to salt to prevent iodine deficiency disorders. It is also a common additive of supplements. Upon ingestion, iodate is reduced to iodide that is absorbed and available metabolically as active iodine[26,27].
- DRI – World Health Organization[44], United Nations Children's Fund and the International Council for Control of Iodine Deficiency Disorders consider a daily intake of 100 μg of iodine per day for adults as being sufficient to provide typical urinary iodine levels of 100 μg/l. This is not the case in the US where the RDA is 150 μg/day for both men and women. The tolerable upper intake level (TUIL) for adults is 1100 μg/day (1.1 mg/day). This is because a large portion of the country is landlocked, and those inhabitants do not consume seafood regularly.
- Many regions throughout the world lack sufficient dietary iodine which is dependent on seafood, particularly salt water fish, and, to a certain extent, milk. It is fortunate that iodine is the simplest micronutrient to fortify; [this] is usually accomplished by the addition of potassium and/or calcium iodate to salt[26,27]. Iodine requirements in pregnancy are higher than for the non-pregnant woman. The RDA must be 220 μg/day to achieve a urinary iodine excretion of >150 μg/day.

Deficiency

- Deficiency is present worldwide and often remedied by fortification,

although this latter process is variable. In the US, addition of iodate to salt began in the 1920s, but as recently as 1988–1994 the National Health and Nutrition examination survey determined that 15% of women aged 15–40 and 17% of pregnant women had urinary concentrations of iodine amounting to only 50 μg, indicating <100 μg daily intake[45].

- Deficiency during pregnancy may be accompanied by catastrophic consequences, including spontaneous abortion, stillbirth and increased perinatal mortality. Newborns may exhibit goiter, mental retardation and cretinism, the most extreme form of neurological damage from hypothyroidism. The brain is particularly sensitive to deficiencies, because thyroid hormones are responsible for myelinization of the central nervous tissue.
- Effect of excess – when the recommended intake is vastly exceeded, the excess intake of iodine may rarely result in goiter, thyrotoxic crisis and hyperthyroidism. This does not occur after digestion of physiological quantities of iodized table salt or from low-dose supplements during pregnancy (1–200 or 100–200 μg/day). WHO recommends upper intake levels of 600 μg/day[46], while the US Institute of Medicine[47] considers the safe upper limit for iodine intake to be 1000 μg/day for pregnant women. Reasons for this wide variation are not clear but illustrate the complexity of attempting to define upper limits of intake that are appropriate for all patients.

Iron

- General – the use of iron in pregnancy has a long history. It was probably first prescribed as a restorative in ancient days in the form of wine (an alcoholic tincture of iron) before the association of alcohol and fetal anomalies was appreciated. Certainly it was known to obstetricians practicing by the middle of the 20th century, at which time it was often prescribed as a separate pill in doses far in excess of what could be reasonably be absorbed and as such was often cited as the cause of gastrointestinal discomfort that ranged from pain and cramps to diarrhea or vomiting. It is not surprising that many women, especially multiparas, are all too happy to deposit their prescriptions for iron products in the waste basket when leaving the clinic or doctor's consultation.
- Iron holds the dubious distinction of simultaneously being an essential trace mineral, the source of the world's most common deficiency, and a potential cause of anemia in pregnancy if its level is insufficient. Its ability to convert between the ferrous (Fe^{2+}) and the ferric (Fe^{3+}) states accounts for its role in oxidative metabolism. When free iron is present, it can lead to the generation of active oxygen species and free radicals that may cause oxidative damage.
- Dietary iron consists of heme and non-heme (inorganic) forms. Heme iron is supplied by meat, fish and poultry, whereas plant-based foods (vegetables, fruits and grains) are the sources of non-heme iron, although bioavailability varies greatly (high from broccoli and cabbage, and low from legumes, rice and maize). Fortified foods always use the non-heme inorganic form, and absorption is enhanced by ascorbate and stomach acid, and inhibited by calcium and a number of food constituents. The average estimated iron absorption from an adequate diet is 10%, a figure that increases to 18% in individuals with depleted stores.
- The numbers cited above relating to absorption cloud the clinical picture. About 4 mg is the maximum that can be absorbed on a daily basis regardless of whether the woman has adequate or inadequate stores. This number is of great importance when advising patients regarding a prenatal supplement that contains iron, because many contain quantities far in excess of that which can be absorbed and which may be the cause of gastrointestinal disturbances.
- Iron status is often measured by hemoglobin levels, with deficiency being defined as <13 g Hb/dl for men and <12 g Hb/dl for women (WHO criteria[48]). There are numerous biomarkers that are better indicators of iron stores, however, especially the total serum iron binding capacity, with levels of more than 450 μg/dl indicating deficiency.
- DRI – the RDA as set by the IOM for pregnancy is 27 mg/day[49]. This represents an approximate 50% increase over the RDA for adult females (18 mg). The need for increased iron is based on the increases in the red cell mass, a 50% expansion of the plasma volume and the growing fetal requirements. Estimations of the amount of iron that needs to be absorbed in the second and third trimester are 4–5 mg/day and 6–7 mg/day, respectively. These needs are partially addressed by existing iron stores even when the woman is anemic. The RDA for lactating women was set at 10 mg/day[26,27].
- Deficiency – although it is clearly beneficial to enter pregnancy with an adequate iron store, WHO estimates anemia is present in 18% of pregnant women in industrialized countries and 56% in developing countries[50]. Most of these anemias had their onset before conception, and the presence of iron deficiencies *per se* as measured by low ferritin far exceeds the prevalence of anemia. The literature on the adverse effects of anemia is copious, with low birth weights, premature delivery and low neonatal iron stores being prominent.

Supplementation

- Given the circumstances described above, it is disconcerting that international organizations have not reached a consensus about the value of supplementation. The recommendations of the Institution of Medicine are complex[51]. The American College of Obstetricians and Gynecologists recommends that all pregnant women should be screened for anemia and those with iron deficiency anemia be treated with supplemental iron in addition to prenatal vitamins[52].
- The authors believe that pronouncements such as these make a simple proposition unnecessarily complex for busy practitioners who often see patients who come for antenatal care with the presumption that they will be given vitamin and iron supplementation. Because most modern prenatal supplements contain rational amounts of iron, it seems reasonable to prescribe them to all pregnant women.
- A final word of caution is necessary. The most common cause of poisoning fatality in young children is accidental

overdose by ingesting iron-containing products. The oral lethal dose is approximately 200 mg/kg, although less can be fatal. Early symptoms include vomiting, nausea, hypotension and respiratory difficulties; later, multiple organ failure or central nervous system (CNS) failure may occur. Maternal oral medications with iron contents clearly should be kept out of children's reach.

- Effect of excess – the upper intake level (UL) is 45 mg/day, a figure based on the likelihood of gastrointestinal distress from higher amounts.

Omega 3 fatty acids

- General – three main types of omega 3 essential fatty acids, with distinctly different functions, are important in perinatal nutrition. Eicosapentaenoic acid (EPA), found primarily in fish and fish oil, helps the body manufacture eicosanoids and has controlling effects on hormones and the immune system, both of which are known to affect brain function. Docosahexanoic acid (DHA) also is found primarily in fish and represents about 97% of all omega 3 fats in the brain and 93% of all omega 3 fats in the retina. As such, it is particularly important for fetal brain and retinal development during the third trimester and up to 18 months of life. DHA is involved in visual and neural function and neurotransmitter metabolism. Alpha-linolenic acid (ALA), found mostly in seeds, vegetable oils and leafy green vegetables, is converted into EPA and then into DHA in the body.
- These omega 3 fatty acids and the omega 6 fatty acid, arachidonic acid (AA), recently have gained attention in the field of prenatal nutrition because of their important functions in fetal and newborn neurodevelopment and inflammation. DHA and AA are critical to fetal and infant central nervous system growth and development[53,54]. All of the omega 3 and omega 6 fatty acids accumulated by the fetus are derived from the mother by placental transfer. During the last trimester, the fetus accrues about 50–70 mg/day of DHA. Both maternal DHA intake and circulating DHA concentrations are important determinants of fetal blood concentrations of DHA.
- Recommendations – pregnant women have an increased need for essential omega 3 fatty acids compared with women who are not pregnant[55]. Supplementation is imperative because pregnant women often do not get adequate omega 3 fatty acids when seafood, the major source, is restricted to two or fewer servings per week. Supplementation is particularly critical for pregnant women who do not have any means of getting omega 3 oils from their diets[56]. No requirements have been established for omega 3s for pregnant women.
- As macronutrients, omega 3s are assigned an AI and AMDR (acceptable macronutrient distribution range) instead of RDAs. The AI for omega 3s is 1.1 g/day for women[57,58], while the AMDR is 0.6–1.2% of total energy[59]. The physiological potency of the various omega 3s differs so widely that it is not possible to estimate one AMDR for all omega 3 fatty acids. Approximately 10% of the AMDR can be consumed as EPA and/or DHA. At the time of this writing, lack of evidence prevents [the] setting [of] a UL (upper tolerable limit) for omega 3 fatty acids[59,60].
- The unified recommendation for pregnant and lactating women is 1200 mg of omega 3s daily. Supplementation is the only way to achieve this, and supplements may be fish oil supplying EPA and DHA or algae-derived DHA in combination with fish oil.
- Omega 3 supplementation in food has become a significant part of food fortification, with food companies around the world launching omega 3 fortified bread, mayonnaise, pizza, yogurt, orange juice, pasta, milk, eggs and confections. In the US, infant formula is regulated as a unique food category by the Food and Drug Administration, and omega 3 enrichment is mandated for all infant formula. This practice increasingly is being adopted by food regulators around the world.
- Excesses – consuming either large or inadequate amounts of omega 3 fatty acids during pregnancy and lactation seems unwise because of the potential for adverse effects on infant development. Whereas evidence shows the detrimental effects of omega 3 deficiency on the health status of babies[61], no evidence has established the effect of consuming excessive amounts of omega 3 during pregnancy or lactation.

Selenium

- General – selenium is an essential trace mineral required only in small amounts[62,63]. Selenium forms selenoproteins with an antioxidant role to prevent cellular damage from free radicals. Selenoproteins also help regulate thyroid function and play a role in immunity[64–66]. The major dietary sources of selenium are plant foods. The selenium content of soil affects the selenium levels in food (plant or animal origin) and food distribution across regions with disparate levels of selenium in the soil helping prevent selenium deficiency in people living in low-selenium geographic areas. Selenium deficiency is, however, a common issue with populations that consume only foods grown locally in low selenium regions.
- Recommendations – pregnant women have a higher need for selenium than do most adults. Food labels do not list selenium content, and the selenium content of foods varies widely depending on food type and area where grown. Because Brazil nuts are unusually high in selenium, with as much as 544 µg per ounce (780% DV [daily value]), it is wise to eat Brazil nuts only occasionally.
- The RDA for pregnant and lactating women is 60 µg and 70 µg selenium, respectively. Information is insufficient to establish an RDA for infants; however, an AI of 15 µg selenium has been established for 0–6-month-old healthy infants who are breastfed and 20 µg for infants 7–12 months old.

Deficiency

- Low selenium levels may be linked to pre-eclampsia, first-trimester miscarriages and recurrent miscarriages[67]. The researchers reported that women with low levels of selenium had up to four times the risk of developing these conditions.
- Selenium deficiency occurs in regions with low selenium soil content,

notably in China and parts of Russia. Selenium deficiency usually does not manifest in illness; rather, it weakens the immune system, rendering the body vulnerable to illnesses caused by other nutritional, biochemical, or infectious diseases. Three diseases are associated with severe selenium deficiency in children: Keshan disease that results in an enlarged heart with poor function, Kashin-Beck disease that results in osteoarthropathy, and myxedematous endemic cretinism that results in mental retardation.

- Women with Crohn's disease and surgical removal of part of the stomach have increased susceptibility to selenium depletion or deficiency, which further exacerbates neurological effects of iodine deficiency on thyroid function[64,68]. Malabsorption owing to HIV/AIDS can deplete levels of selenium, and selenium deficiency is associated with decreased immune cell counts, increased disease progression, and mortality in HIV/AIDS populations[69,70], so much so that physicians often prescribe selenium supplements as part of an overall maternal nutrition plan for such patients.

Supplementation

- Selenium occurs in foods as selenomethionine and is incorporated into body proteins along with the methionine. On the market, selenium supplements often are based on sodium selenite and sodium selenate, forms that are not absorbed or utilized as optimally as is the organic form. "High selenium yeasts" contain as much as 1000–2000 μg of selenium organically bound per gram[71] and are more effective because of greater bioavailability. Only high-selenium yeast has been shown to lower cancer incidence and prostate specific antigen (PSA) and is recommended over the organic form for supplementation.
- European crop survey data indicate selenium levels in British and European wheats to be generally 10–50 times lower than in American or Canadian wheats. Thus, foods made from such wheat, a staple grain for example, would fail to help consumers meet the recommended intake of selenium. Despite this, no uniform regulations mandating enrichment of staple foods with high-selenium yeast are available on a worldwide basis.
- Excess – high blood levels of selenium (>100 μg/dl) can result in a condition called selenosis[72], the symptoms of which include gastrointestinal upsets, hair loss, white blotchy nails, garlic breath odor, fatigue, irritability and mild nerve damage[62]. Selenium toxicity is rare.

Vitamin A

- General – vitamin A is a fat soluble nutrient that exists in several forms (known as retinoids), including retinol, retinal, retinoic acid and retinyl ester. Synthetic analogues also exist, as do about 600 provitamin A carotenoids that represent precursors of vitamin A. Only about 10% of the latter compounds can be converted to vitamin A, although both types are found in nature. Vitamin A is primarily present in animal-origin food stuffs, especially liver, dairy products (whole milk, cheese and butter), and fish, such as tuna, sardines and herring. Fish liver oils, in particular cod liver oil, are also high in vitamin A content. Carotenoids are synthesized by plants and found mainly in fruits and vegetables, the most abundant of which is beta carotene that has the greatest amount of provitamin A activity. Vitamin A is essential for vision, reproduction, immunity, skin and epithelial integrity, and the transduction of light into neural signals in the eyes. It is especially critical during periods wherein cells rapidly proliferate and differentiate.
- DRI – in 2001, the Institute of Medicine revised the RDA guidelines for vitamin A expressed as retinol activity equivalents (RAE)[73]. No such action was taken for carotenoids because they are not considered essential nutrients. The RDA for pregnant women is 750–770 μg RAE in which 1 μg of retinol equals 12 μg beta carotene. The tolerable upper intake (UL) is 3000 μg for preformed vitamin A. Doses of vitamin A present in supplements are usually reported in IU and need conversion to RAE to determine whether they meet the RDA.
- During pregnancy, requirements are predictively higher because of fetal growth needs. In well-nourished women, diet suffices to provide suggested requirements[74].

Deficiency

- Although deficiencies are rare in industrialized nations, they represent a major problem globally, and are most commonly manifest as night blindness and xeropthalmia. In pregnancy, especially during the third trimester, vitamin A starts to accumulate in the fetus. No correlation between deficiency and malformed infants has been established. After the first few weeks of life, neonatal deficiency may develop if the breastfeeding mother is vitamin A deficient.
- Toxicity – case reports of offspring with anomalies after mothers took high levels of vitamin A[75,76] have led to some concern about high doses during pregnancy. Although no consistent pattern of anomalies has been observed[74], caution has been raised against any dose greater than 2500 IU. The literature on anomalies is unclear, because doses have varied from 10,000 IU daily to 50,000 IU in the form of a supplement. Even when 10,000 IU was the dose utilized, the literature is divided as to whether increases in anomalies are seen[26,27]. In contrast to the equivocation regarding the effects of excess vitamin A, the literature is clear that retinoid analogues cause birth defects or embryonic demise, with pronounced teratogenicity ascribed to synthetic analogue 13 cisretinoic (isotretinoin), a compound used in a specific medication (Accutane) that is highly effective for severe cystic acne and may be used by women of reproductive age. The US FDA requires that female patients be informed that two types of contraception be used when retinoid drugs are prescribed[77]. Pregnancy should be avoided during drug administration and for 3 months thereafter, because the likelihood of deleterious effects is among the highest of the known teratogens. In contrast to the retinoids, toxicity because of beta carotene and other keratonoids in food is not considered a concern, and for this reason no UL has been set.

Supplementation

- Many authorities are of the opinion that vitamin A supplementation is not warranted in healthy women except perhaps in developing countries were deficiency is a problem. In such instances, the maximum daily supplement of vitamin A advised by World Health Organization is 300 µg or 10,000 IU[26,27].

Vitamin B3 (niacin)

- General – vitamin B3 or niacin (also known as, nicotinic acid and vitamin PP) is an essential human nutrient, other forms of which include the corresponding amide, nicotinamide or 'niacinamide'. The terms niacin, nicotinamde and vitamin B3 are often used interchangeably to refer to any member of this family of compounds, since they have the same biochemical activity. Niacin is converted to nicotinamide *in vivo* and, although the two are identical in their vitamin activity, nicotinamde does not have the same pharmacological effects as niacin. Nicotinamide does not reduce cholesterol or cause flushing. Niacin is involved in DNA repair and the production of steroid hormones in the adrenal gland.
- Niacin is found in a variety of foods including liver, chicken, beef, fish, cereal, peanuts and legumes, and is also synthesized from trytophan, which is found in meat, dairy and eggs. Niacin may also be derived from seeds and nuts, whole grains and enriched whole grain products, as well as from mushrooms and spent brewer's yeast (Vegemite or Marmite).
- The recommended daily allowance of niacin is 14 mg/day for women and 18 mg/day for pregnant or breast-feeding women. The upper limit for adult women is 35 mg/day, which is based on flushing as the critical adverse effect.
- In larger doses, niacin can reverse atherosclerosis by lowering low-density lipoprotein (LDL) and favorably affecting other compounds. In general, niacin status is tested through urinary biomarkers, which are believed to be more reliable than plasma levels.

Deficiency

- Severe deficiency of niacin is associated with a pandemic deficiency disease called pellagra. Pellagra is characterized by diarrhea, dermatitis and dementia, as well as 'necklace' lesions on the lower neck, hyperpigmentation, thickening of the skin, inflammation of the mouth and tongue, digestive disturbances, amnesia, delirium and eventually death, if left untreated. Niacin deficiency is rarely seen in developed countries, but it is apparent in conditions of poverty, malnutrition and chronic alcoholism. It tends to occur in areas where people eat maize or corn – the only grain low in niacin – as a staple food. A special cooking technique called nixtamalization is employed to increase the bioavailability of niacin during maize meal or masa production.

Supplementation

- The RDA for niacin is 18 mg for adult men and 14 mg for adult women, although more is needed for nursing (20 mg) and pregnant women (18 mg).
- Pharmacological doses of niacin (1.5–6 g/day) often cause skin flushing and itching, dry skin, skin rashes and gastrointestinal complaints, such as dyspepsia (ingestion). High-dose niacin may also elevate blood sugar, thereby worsening diabetes mellitus and gestational diabetes.
- Niacin at doses used in lowering cholesterol (>35 mg/day) has been associated with possible consequences for infant development, nausea and vomiting in pregnant women.

Vitamin B6

- General – vitamin B6 consists of a family of seven substituted pyridine derivatives, the major forms in tissue being pyridoxal phosphate (PLP) and pyridoxamine phosphate (PMP). The others are: pyridoxine (PN), the form that is given as vitamin B6 supplement; pyridoxal 5'-phosphate (PLP), the metabolically active form; pyridoxamine (PM); pyridoxamine 5'-phosphate (PMP); and 4-pyridoxic acid (PA), the catabolite which is excreted in the urine.
- All forms except PA can be interconverted. Bioavailability of B6 supplements is in excess of 90%, whereas food vitamin B6 is >75% bioavailable. Cereals, meat, fish and non-citrus fruits are the major contributors of vitamin B6. Rich sources include fortified cereals, beef liver and other organ meats.

Deficiency

- Overt clinical symptoms attributable to vitamin B6 deficiencies are rare. Numerous studies have assessed a variety of populations in an attempt to determine deficiency. Lack of supporting clinical evidence of deficiency makes it questionable whether biochemically defined relative deficiencies represent true vitamin B6 deficiencies.
- Pregnancy – maternal levels of B6 status as found in plasma/whole blood decrease as the gestation advances but more so in the last trimester. Whether observed changes represent poor vitamin status or physiological changes is not clear, because no clinical evidence of significant problems in vitamin B status is available even in the presence of levels of status markers. The only evidence suggesting doses in the range of 4–10 mg of pyridoxine are the few studies suggesting the APGAR scores of infants are higher when mothers take supplements containing more than 5 mg of pyridoxine[26,27].
- The limited number of studies regarding benefits of vitamin B6 and pregnancy complications are inconclusive, although these same supplements have been used to treat hyperemesis gravidarum for decades, usually in doses of 100 mg or more. Today pyridoxine is usually but not always given in combination with doxylamine. Controlled studies show a very effective response to pyridoxine, although the placebo often is equally as effective. In summary, supporting evidence for its effectiveness when administered alone is weak[26,27].
- Teratogenicity – older literature suggests that vitamin B6 can exert teratogenic effects of a variable nature in animals; however, this concern is of a limited nature in humans, primarily based on the extensive literature

relating to the combination of the antihistamine doxylamine and pyridoxine that was marketed worldwide for years for use during pregnancy as a treatment against nausea and vomiting.

Supplementation

- DRI – the RDA for the adult was set at 1.3 mg/day. The RDA for pregnant and lactating women was increased to 1.9 and 2.0 mg/day, respectively, based on an average estimated accretion by the placenta and fetus in addition to increased maternal metabolic demands through pregnancy of about 0.25 mg/day, mostly occurring in the second half of gestation. The median intake from food sources in the US was estimated at 2 mg for men and 1.5 mg for women of vitamin B6[26,27].
- Effect of excess – the IOM has set an upper limit of 100 mg/day of vitamin B6. Severe sensory neuropathy has been reported in individuals ingesting very large doses of pyridoxine (1–6 g/day) with some evidence of adverse effects at 500 mg/day. No credible adverse effects have been noted at doses of 300 mg or less[26,27].

Vitamin B12 (cobalamin)

- General – vitamin B12 (cobalamin) is an important co-factor for two key enzyme reactions – methionine synthase and L-methylmalonyl-CoA mutase. It is found only in foods of animal origin, and major dietary sources include but are not limited to red meat, chicken, fish, milk, yogurt, cheese and liver[78]. Dietary B12 possesses only approximately 50% of the bioavailability of crystalline synthetic B12[43]. Although synthetic B12 is used to fortify certain food products such as breakfast cereals, it is not one of the nutrients required to be added to the so-called enriched grain products used in the US and Canada[26,27].
- DRI – clinical symptoms of deficiency (neurological, cognitive, hematological) usually occur with serum or plasma levels <148 pmol/l; biochemical signs of inadequacy begin when plasma/serum blood levels are <221 pmol/l. Accordingly, recommended cutoffs for diagnosing B12 deficiency and depletion are <148 pmol/l (200 pg/ml) and <221 pmol/l (<300 pg/ml) in plasma or serum.

Deficiency

- General population – deficiency primarily results from low intake of animal-based foods or food-bound vitamin B12 with infrequent causation by pernicious anemia. The former deficiency most usually occurs in individuals older than 50 years of age, whereas malabsorption results from either decreased acid reduction or pancreatic insufficiency. Pernicious anemia results from the lack of intrinsic factor required for uptake of B12 into the intestinal lumen[78]. It is rarely seen in women of reproductive age.
- Population-based data from the US indicate that 16% of individuals aged 19–50 years of age are either deficient (<148 pmol/l) or marginal (149–221 pmol/l). Avoiding consumption of all animal-based foods (strict vegan) is not necessary to develop deficiency, and deficiency is more prevalent in the general population than previously thought. For example, a Canadian study of 10,622 women aged 15–46 found an overall prevalence of B12 deficiency of 7.4%[79], with a chemical deficiency (<125 pmol/l) present in 6.9% of non-pregnant women, 5.2% of those pregnant <28 days, and 10.1% of those pregnant >28 days.
- Infants commonly become B12 deficient because their mother's diet was restricted before pregnancy, during gestation, or during lactation[80]. Thus, pregnant women who limit consumption of animal-based products may have impaired vitamin B12 status that negatively affects delivery of sufficient B12 to the embryo[81]. Prenatal vitamin B12 supplementation is advisable for women who are not willing to increase their consumption of vitamin B12-containing food.
- Teratogenic effects – vitamin B12 deficiency is an independent risk factor for pregnancy complications and birth defects. Most often these defects mimic those found with folic acid deficiency. In particular, Irish investigations have provided strong support for a correlation between lower vitamin B12 status, independent of folate status, and an increased NTD risk in a population not exposed to folic acid fortification or supplement[82]. Specifically, Irish mothers with serum B12 concentrations in the lowest quartile had a 2–3-fold higher AOR [adjusted odds ratio] for having an NTD-affected infant compared to those in the highest quartile.
- Breastfeeding mothers who are vitamin B12 deficient are liable to have infants who, over time, show lethargy, irritability, or developmental delay if their mothers adhere to a vegan or vegetarian diet. Neonatal neurological abnormalities second to subacute combined degeneration of the spinal cord may be irreversible.

Supplementation

- The RDA for vitamin B12 is 2.4 μg/day[43]. During pregnancy, this increases by 0.2 μg/day, so that the RDA for pregnancy was set at 2.6 μg/day by the IOM in 1998.
- Effect of excess – there is no evidence that excess vitamin B12 has a teratogenic effect, and no reports of vitamin B12 toxicity exist in the general population or during pregnancy.

Vitamin D

- General – there are two chemical forms of vitamin D. Vitamin D2, ergocalciferol, is synthesized by plants. Vitamin D3, cholecalciferol, is synthesized by mammals. Dietary sources of vitamin D are numerous and primarily come from animal origin (liver oils and fatty fish such as salmon, herring and tuna). Many foods, including milk, yogurt, cheese, margarine and some brands of breakfast cereal are fortified with vitamin D. In the US, milk and selected brands of orange juice are fortified with 100 IU vitamin D per 8 oz.
- The primary source of vitamin D is the skin where ultraviolet light-B converts 7-dehydrocholesterol under the influence of exposure to sunlight. This is of particular importance for individuals living in northern latitudes with limited sunlight, in populations with heavily pigmented skin,

and in populations who cover exposed skin for religious or cultural reasons[83]. Serum 25-(OH) D3 is the best indicator of vitamin D status. Deficiency is defined in adults as serum/plasma concentrations of 25-(OH) D3 <50 nmol/l, although it is recognized that various investigators define this value differently.

- DRI – no RDA has been established because of lack of sufficient data; however, the AI for men and women (19–50 years of age) is 5 μg/day (200 international units)[43]. This value may be too low and possibly will be modified in the near future.

Deficiency

- General population – in non-pregnant women, vitamin D deficiency is not uncommon, although prevalence rates differ markedly on a racial basis (42% in African American women vs. 4% in white women). Part of this discrepancy may be on a genetic basis, because prevalence remains high (19%) among African American women who consume >200 IU vitamin D per day from supplements and eat fortified cereal >3 times/week. Such findings suggest that the AI may need adjustment on a "racial/ethnic basis"[26,27].
- Pregnancy – in general, 25–30 g calcium is transferred from the mother to the fetal skeleton, primarily during the latter stages of pregnancy. Under these circumstances, vitamin D deficiency during pregnancy may result in adverse outcomes in the fetus that persist long term, including rickets. Numerous studies of the maternal-fetal dyad have been conducted in the US and the UK from which there are several general conclusions: (1) pregnant women and their neonates who live in northern latitudes are at higher risk of vitamin D deficiency than are those who live in southern latitudes; (2) women with darker skin colors exhibit greater levels of deficiency than do women with lighter skin colors (this includes African Americans and many Hispanics of mixed race in the US and Africans, Indians and Caribbean islanders in the UK); (3) seasonal variations contribute little to vitamin status changes, particularly in women of color and their neonates; (4) current formulations of prenatal vitamin supplements may be inadequate to achieve desired serum levels of 25-(OH) D3; and (5) interconceptional intervals are too short.

Supplementation

- Evidence is rapidly accumulating that, in contrast to published guidelines, vitamin D supplementation may be necessary for all patients to achieve the desired 25-(OH) D3 concentration of >50 nmol/l in pregnant women. As recently as 2008, Wagner *et al*.[84] recommended assessing maternal vitamin D status by measuring 25-(OH) D3 concentrations in pregnant women to be followed by supplementation in the case of deficiency. However well meaning this advice, it is, in the opinions of the authors, impractical. We believe, from a public health point of view, that supplementation of higher amounts is more practical, because vitamin D in therapeutic doses does not appear toxic. A dose of 250 μg/day appears safe and represents the amount that can be synthesized only by total body sun exposure.

Zinc

- General – another essential trace element is zinc, which plays a structural and/or catalytic role in more than 300 enzymes and proteins involved in growth and development, neurological function, the immune system and reproduction.
- Bioavailability of zinc varies widely, with rich sources found in red meat, oysters and whole grains – primarily in the germ and bran, so milling or polishing grains such as rice leads to loss of most of the nutrients. Bioavailability is improved in vegetarian diets containing refined or fermented grains.
- Most zinc is stored in skeletal muscle and bone with primary losses in feces and only a small amount in urine, skin and hair. Zinc status indicators are lacking.
- DRI – the RDA is 8 mg for adult women, assuming 70% is absorbed from meat. In contrast, World Health Organization publishes two RDAs for adults, 5.6 mg/day for meat eaters and 18.5 mg/day for vegetarians. During pregnancy, the RDA is increased to 11 mg for adult women and 13 mg for pregnant teenagers. The upper limit is 40 mg/day for women and 34 mg/day for teenagers[85].

Deficiency

- Zinc deficiency is rare in North America but may be prevalent in other countries (Middle East and Latin America) and associated with impaired growth and development. Zinc bioavailability from vegetarian diets is lower than from non-vegetarian diets because vegetarians do not eat meat, which is naturally high in bioavailable zinc. Additionally, vegetarian diets are typically high in legumes and whole grains that contain phytates binding zinc and inhibiting its absorption. Vegetarians sometimes require as much as 50% more of the RDA for zinc than do non-vegetarians.
- Results of studies of poor zinc status in pregnancy are unclear, with adverse fetal outcomes being reported as congenital anomalies and preterm deliveries along with pre-eclampsia, hemorrhage, infections and prolonged labor. Randomized controlled intervention trials in pregnancy are mixed, in that half show positive effects and half show no effects in terms of growth retardation, preterm delivery, and increased birth weight.

Supplementation

- Evidence supporting the benefits of supplementation is mixed, although it is believed that supplementation with 15 mg/day in pregnancy may provide some benefit, especially for those whose diets contain food which have poor zinc availability[26,27].
- Teratogenicity – it is not clear whether zinc deficiency causes human structural malformations[86], because much of the early literature fails to consider decreased maternal folate levels as a confounder[26,27].'

SUMMARY

This chapter reminds readers of the important relationship between maternal diet and fetal outcome, comments on the difficulties of obtaining an adequate and nutritious diet in a modern society, and stresses that dietary inadequacies that existed before pregnancy cannot be rectified once pregnancy has begun. This latter point is illustrated by consideration of folic acid, which only recently has been recognized as being required in pre-pregnancy so the mother has adequate amounts during the critical time of neural tube formation in the first 28 days after conception.

A major problem facing today's health-care practitioners in terms of counseling their pregnant patients regarding diet and nutrition is that the available source documents vary so widely in their points of view. This is particularly true in the literature relating to supplementation, in which it is the rare article that mention its biases. This is unfortunate, because the biases and the context around which an article is written may never be understood by the public. For example, as our editorial team was finalizing this chapter, the senior author (LK) received a newsletter from an internationally renowned university directed to women. The lead article stated that obtaining one's micronutrients in pregnancy through diet requires planning, patience and knowledge about foods, in particular nutrient-dense foods (those packed with vitamins and minerals with relatively few calories). The article listed 18 nutrient-dense foods, most of which are not eaten by the general population, let alone pregnant women: leafy vegetables such as chard, collard greens, kale and mustard greens; brussels sprouts; crimini and shitake mushrooms; papaya; flax seeds; garbanzo and pinto beans; almonds; barley; oats; quinoa; halibut; and venison. Sample menus listed sliced kiwi, edamame, walnuts and salmon (commonly listed as a fish that supplies omega 3 oil, even though mackerel is a much richer source). We believe that this advice, however well meaning, is disingenuous at best, because it does not address the real needs of patients but rather presents them with theoretical solutions for problems over which they have little control.

That diets have changed in the past 150 years was described in great detail in a three-part series in the *Journal of the Royal Society of Medicine*[87–89]. Here the authors were careful to relate such changes to the social context that surrounded them, which included an increasing reliance on transportation as opposed to walking, the advent of refrigeration and food preservation, and incorporating ethnicities into UK society who brought their foods with them.

Physicians must view pregnant patients (and the diets they ingest) in the context of the society in which these patients live. This includes nuclear households of one or two, the necessity of two-income households, the demands of work and outside interests on available time, and the easy availability of food prepared outside the home. It is unrealistic to think that pregnant women eat all meals prepared at home, have the time or resources to shop and look for the exotic foods that may be nutrient dense and vitamin rich, and never resort to fast food or 'take out'. Also, it is important to remember that food choices often are based on inherent tastes, that tastes are at least to some degree related to culture, and that cultural food choices are intergenerational.

So where does that leave the physicians and the patients they serve? The simple answer relates to supplementation. If one is not inherently biased against supplementation, it is not difficult to envision circumstances whereby supplementation becomes a lifelong habit in which supplements change as the individual ages and life circumstances change. Thus, discussions of supplementation need not be confined to pregnancy alone but can be initiated during active teenage years and certainly when marriage and childbearing are anticipated.

Once supplementation is begun, it can be continued into lactation and the time between pregnancies, and maintained through and after menopause into the senior years with the caveat that supplements which are ideal for a teenager need to be changed for the geriatric population.

Although individuals eat to taste, they generally do not eat one or two nutrients on an exclusive basis. Thus, it is disheartening to see reports of pregnant women receiving high doses of single vitamins in the hope that this will be of therapeutic value. In the same sense, it is not surprising when trials using high doses of single vitamins do not achieve their desired goals. If health-care professionals advise patients to eat a balanced diet consisting of fruits, vegetables, meat, fish, grains, fat, etc., they should have no difficulty in strongly advising them to select high quality multivitamin, mineral and micronutrient supplements that represent a balanced palate of what is needed before, during and after pregnancy.

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23
Drugs to avoid preconceptionally

Vivek Nama and Hassan Shehata

Pharmacologic agents are unnecessary for normal pregnancy; however, some women plan pregnancy with medical conditions that require continuing or episodic treatment (e.g. asthma, epilepsy and hypertension). Moreover, during the reproductive years and during pregnancy, new medical problems may develop, and old ones can worsen (e.g. migraine headaches), to the extent of warranting pharmacologic therapy. In addition, many women consume prescribed and/or over-the-counter (OTC) medications during pregnancy[1,2]. A comparison of therapeutic drug usage in pregnancy across Europe documented that 64% of women used at least one drug during their pregnancy[3], while, in France, pregnant women were prescribed an average of five drugs during the first trimester[2]. In the UK about one-third of women take pharmacological agents at least once in pregnancy, whereas only 6% take these agents in the first trimester[4]. Whereas it is plausible to collect data regarding the usage of medications in the preconception period, it would not be wrong to imagine that such usage is higher than the rates that have been documented in pregnancy.

Preconceptional counseling on the use of medications is of importance, as the consumption of medications is on the rise, new products are being marketed directly to the consumer and more prescription medications have been granted non-prescription status by the US Food and Drug Administration (FDA). Though not widely practiced, unfortunately, drug regimens prescribed for chronic illnesses are best altered preconceptionally. In all probability, at least 10% of birth defects can be attributed to maternal drug exposure in pregnancy[5].

COUNSELING FOR THE EXPECTANT MOTHER

The expectant mother should be counseled as to whether to continue or initiate a new medication in an open, supportive and informative manner. Most conditions that require medication involve drug exposures at low levels of relative and absolute risks. The goals of preconception medical management include: identifying patterns of medication and supplement use prior to conception; counseling women with chronic conditions about the potential impact of the condition and its various treatments on maternal and fetal health; establishing effective treatment for chronic conditions before conception; and counseling women to avoid the use of non-essential medications and OTC medications. Table 1 describes simple strategies for prescribing medication preconception and during pregnancy. Factors that affect the action(s) of the drug should be understood, including the FDA risk stratification of drug usage in pregnancy before prescribing (Table 2) and counseling an expectant mother.

Table 1 Useful strategies for prescribing medications in pregnancy and preconception

Avoid multiple medications if possible and choose those that are 'safe' (anticonvulsants, antihypertensives) and in the smallest dose possible
Determine what is the best method to monitor therapy (asthma: peak flow meters; hypertension: portable blood pressure monitors; diabetes: glucometers)
The healthiest mother is most likely to deliver the healthiest infant
Focus on the underlying disorder, not on the drug alone, to explain any additional risk to the fetus (hypertension and fetal growth restriction, seizures and childhood seizures, systemic lupus and fetal growth restriction)
Only a few drugs are clearly linked with specific birth defects (phenytoin, warfarin, alcohol, methotrexate, diethystilbestrol, cis retinoic acid, valproic acid, carbamazepine)
Experience with first trimester exposure for any drug is often too limited in humans to be considered 'safe'

Table 2 US FDA pregnancy category definitions

Category	*Description*
A	Controlled studies in women fail to show a risk to the fetus in the first trimester, and the possibility of fetal harm appears remote
B	Animal studies do not indicate a risk to the fetus and there are no controlled human studies, or animal studies do show an adverse effect on the fetus but well controlled studies in pregnant women have failed to demonstrate a risk to the fetus
C	Studies have shown the drug exerts animal teratogenic or embryocidal effects, but there are no controlled studies in women, or no studies are available in either animals or women
D	Positive evidence of human fetal risk exists, but benefits in certain (for example, life-threatening or serious diseases for which safer drugs cannot be used or are ineffective) may make use of the drug acceptable despite its risks
X	Studies in animals or humans have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, or both, and the risk clearly outweighs any possible benefit

FACTORS AFFECTING THE EFFECT OF DRUGS DURING PRECONCEPTION

Safety information data

The safety and efficacy of drugs at a given dosage regimen is established by phase 3 clinical trials, involving numerous and typical representatives from the target patient population. Pregnant women and those who fall pregnant during the trial are excluded from such studies. Thus, at a drug's first marketing, except for products developed to treat conditions specific to pregnancy such as oxytocics and/or cervical ripening agents, human data on the proper dosage and frequency of administration during pregnancy seldom exist. All medications approved by the FDA must undergo animal studies to determine possible teratogenic effects. Doses (per body weight or surface

area) are often much higher than typically used to determine possible detrimental reproductive harm. Although such studies may be helpful, especially if findings indicate no additional risk, their results do not reliably predict the human response.

Pharmacokinetics of drugs in pregnancy

The physiological changes during pregnancy exert a marked impact on drug pharmacokinetics and hence established therapeutic ranges might be inappropriate. Pharmacokinetic changes during pregnancy include a higher volume of distribution, lower maximum plasma concentration, lower steady serum state concentration, shorter plasma half-life and higher clearance rate. As the placenta essentially acts as a lipid barrier between the maternal and fetal circulations and drugs cross it by passive diffusion, transfer of drugs to the fetus is unavoidable. In this regard, low molecular weight, lipid soluble and unionized drugs cross the placenta more readily than polar drugs.

Human teratogenesis

Teratogenesis is defined as structural or functional dysgenesis of the fetal organs. Typical manifestations include congenital malformations with varying severity, intrauterine growth restriction (IUGR), carcinogenesis and fetal death. Lack of understanding of the full and exact mechanisms of teratogenicity makes it difficult to predict, on pharmacological grounds, that a given drug will produce congenital malformations. Confirmation of pregnancy and accurate gestational dating are critical in determining susceptibilities, and 'all or none' effect (spontaneous abortion or not) is believed to result from exposure during the ovum period (fertilization to implantation). In contrast, the embryonic period (implantation to 8th week of gestation) involves organogenesis and encompasses the most critical time with respect to structural malformations. Whereas specific harmful effects relate to the timing and duration of drug exposure during this relatively brief but critical time of development, information in humans is minimal or inconsistent regarding long-term effects, such as learning or behavior problems (functional teratogenesis) that may result from chronic prenatal exposure to given medications.

This chapter provides a quick reference guide for drug use in pregnancy. The drugs listed here are in groups according to how they appear in the WHO 11th Model List of Essential Drugs. A quick reference guide of drugs contraindicated in pregnancy (category X) is listed in Table 3.

ANESTHETICS

General anesthetics

Intravenous anesthetics induce anesthesia rapidly; common examples are thiopentone and propofol, though the latter has not been used during the first and second trimesters in humans. Reproduction studies in rats and rabbits at doses six times the recommended human induction dose revealed no evidence of impaired fertility or fetal harm.

Commonly used inhalation anesthetics include halothane and nitric oxide. Halothane can induce hepatotoxicity, and because of its property of relaxing the smooth uterine muscle it increases the risk of postpartum hemorrhage. The Collaborative Perinatal Project[6] showed no embryonic or fetal effects associated with use of nitric oxide. Use during delivery, however, leads to neonatal depression

and fetal accumulation of nitric oxide, which increases over time. Therefore it is safer to keep the induction to delivery time as short as possible.

Neuromuscular blocking agents

These agents are used as adjuncts to anesthetics in order to provide muscle relaxation. Based on mechanism of action, they are divided into depolarizing and non-depolarizing agents. Succinylcholine is the only depolarizing agent commonly used. The Collaborative Perinatal Project[6] recorded 50,282 mother-child pairs, 26 of whom had first trimester exposure to succinylcholine. No congenital malformations were observed in any of the newborns.

ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS, DRUGS USED TO TREAT GOUT AND DISEASE-MODIFYING AGENTS USED IN RHEUMATIC DISORDERS

Non-opioid analgesics, antipyretics and non-steroidal anti-inflammatory drugs

Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) do not produce structural defects. Salicylates (in analgesic doses) and NSAIDs may increase the risk of neonatal hemorrhage by inhibition of platelet function. NSAIDs may also lead to oligohydramnios by their effect on the fetal kidney. The use of NSAIDs in the last trimester causes premature closure of the ductus arteriosus leading to neonatal primary hypertension. Both premature closure of the ductus and the oligohydramnios are reversible. If used during pregnancy, NSAIDs should be discontinued at least 6–8 weeks before delivery.

Table 3 Examples of contraindicated drugs and their known adverse effects on the developing human fetus

Drugs	*First-trimester fetal effects*	*Second- and third-trimester fetal effects*
Quinolones	Toxic to developing cartilage	
NSAIDs		Cardiac, gastroschisis, miscarriage, premature ductal closure
Methotrexate	Miscarriage, cranial anomalies	IUGR
Immunosuppressants	Embryopathy	
Doxycycline		Effect on bone growth
I-131	Fetal thyroid development, CNS development	
Chemotherapeutics	Abortion, anomalies	Hypoplastic gonads, IUGR
Antabuse	Congenital malformations	
ACE inhibitors	Cardiac/CNS malformations	Oligohydramnios, IUGR, renal failure
Retin-A derivatives	CNS, cardiac, facial anomalies	Stillbirth, mental retardation
Streptomycin	Otoxicity	None known
Tetracycline	None known	Staining of teeth
Thalidomide	Limb reduction (gastrointestinal/ cardiac/renal defects)	
Warfarin	Skeletal defects CNS defects	Microhemorrhages

IUGR, intrauterine growth retardation; ACE, angiotensin converting enzyme; CNS, central nervous system

Opioid analgesics

In a surveillance study of Michigan Medicaid recipients, 375 (4.9%) major birth defects were noted (325 expected)[7]. Specific data were available for six defect categories, including (observed/expected) 74/76 cardiovascular defects, 14/13 oral clefts, 4/4 spina bifida, 25/22 polydactyly, 15/13 limb reduction defects and 14/18 hypospadias. Only with the total number of defects is there a suggestion of an association between codeine and congenital defects, but other reasons, including maternal disease, concurrent drug use and chance may be involved. In an investigation of 1427 malformed newborns compared with 3001 controls, first trimester use of narcotic analgesics (codeine most commonly) is associated with inguinal hernias, cardiac and circulatory defects, cleft lip and palate, dislocated hip and other musculoskeletal defects. These data serve as a possible warning that indiscriminate use of codeine may present a risk to the fetus. Use of codeine during labor produces neonatal respiratory depression to the same degree as other narcotic analgesics. Neonatal codeine withdrawal has also been reported[8].

Drugs used to treat gout

Colchicine is used to treat the pain of acute gouty arthritis attacks and as prophylaxis for recurrent gout attacks. It is also used in familial Mediterranean fever, Behcet's disease and amyloidosis. It is embryocidal in mice and rabbits, but the risk of teratogenesis in humans is unknown. It is possible that colchicine given around the time of conception may result in an increased frequency of trisomy 21 in the offspring by causing chromosomal nondysjunction. If used around conception, fetal karyotyping is recommended. In a couple planning a pregnancy colchicine ingestion by either parent should be discontinued 3 months before conception[7].

Disease-modifying agents of rheumatic disorders

Sulfasalazine

Sulfasalazine and its metabolite, sulfapyridine, readily cross the placenta to the fetal circulation. No increase in human congenital defects or newborn toxicity has been observed from its use in pregnancy. Milk concentrations are roughly 40–60% of maternal serum levels. Bloody diarrhea in an exclusively breastfed infant was attributed to the mother's sulfasalazine therapy (3 g/day). Cautious use of sulfasalazine is recommended in nursing women because of significant adverse effects in some nursing infants.

Cyclophosphamide

Various abnormalities ranging from karyotyping abnormalities to multiple structural anomalies have been described with the use of cyclophosphamide in the first trimester. Use of cyclophosphamide in the second and third trimesters does not place the fetus at risk for congenital defects. Except in a few individual cases, long-term studies of growth and mental development in offspring exposed to cyclophosphamide during the second trimester, the period of neuroblast multiplication, have not been conducted. Cyclophosphamide is contraindicated during breastfeeding because of a reported case of neutropenia and because of the potential adverse effects of immune

suppression, fetal growth retardation and carcinogenesis.

ANTICONVULSANTS/ANTIEPILEPTICS

Phenytoin, primidone, phenobarbitone, carbamazepine and sodium valproate all cross the placenta and are teratogenic. The major abnormalities produced by anticonvulsants are neural tube, orofacial and congenital heart defects. Neural tube defects are mainly caused by sodium valproate (1–2%) and carbamazepine (0.5–1%). Orofacial defects are mainly from phenytoin, which also produces the fetal hydantoin syndrome. The syndrome includes prenatal and postnatal growth restriction, motor or mental deficiency, short nose with broad nasal bridge, microcephaly, hypertelorism, strabismus, epicanthus, wide fontanelles, low-set or abnormally formed ears, limb deformities, nail and distal phalange hypoplasia, hypospadias, hernia, webbed neck, low hairline, impaired neurodevelopment and low performance scores on tests of intelligence. Phenytoin and sodium valproate also produce heart defects. Primidone produces abnormalities similar to those produced by phenytoin.

The risk for any single drug is about 6–7% (i.e. two to three times the background level). The risk increases with multiple drugs. Patients on two or more anticonvulsants carry a risk of 15%, and for those taking a combination of valproate, carbamazepine and phenytoin the risk is as high as 50%. The risk of neural tube defects may be decreased with consumption of preconceptional and first trimester folic acid at a dose of 5 mg/day, i.e., more than 10 times the recommended dose of 400 μg/day for normal pregnant woman. Because the newer anticonvulsant drugs such as vigabatrin, lamotrogine, topiramate and gabapentin are often prescribed in combination with other anticonvulsants, it is difficult to ascertain the teratogenic risk of these agents in isolation. Monotherapy should be used wherever possible, and special care should be taken to keep doses as low as possible and compatible with seizure prophylaxis. To lower the risk of hemorrhagic disease of the newborn, vitamin K (10–20 mg orally) should be prescribed for all epileptic women on enzyme-inducing drugs in the last 4 weeks of pregnancy.

The traditional anticonvulsants, such as phenytoin, carbamazepine and valproic acid, are considered safe for use during breastfeeding; however, observation for adverse effects such as drowsiness is recommended for women receiving high doses. The use of phenobarbital with breastfeeding is controversial because of its slow elimination by the infant. Data are sparse regarding the long-term effects of newer antiepileptic drugs on cognition and behavior when used in pregnancy and lactation.

ANTI-INFECTIVE DRUGS

Antihelminthics: intestinal antifilarials, antischistosomals and antitrematode drugs

Mebendazole

Mebendazole is a broad spectrum antihelminthic agent effective in the treatment of ascariasis, enterobiasis, trichuriasis and hookworm disease. It is embryotoxic and teratogenic in rats, and is therefore not recommended for use during pregnancy.

Albendazole

The observation of limb reduction defects at all doses in one animal study, potential for higher plasma concentrations of the metabolite if consumed with a fatty meal, and limited human pregnancy data all suggest that use of albendazole during pregnancy is not recommended. Data on the safety of albendazole in breastfeeding are lacking.

Praziquantel

Praziquantel is not a teratogen in animals, but there are few human data. Recent data indicate that the agent may be mutagenic and carcinogenic in humans, especially in developing countries where infections of trematodes and cestodes are frequent and multiple treatment courses may often need to be prescribed. Because of this potential toxicity, the use of praziquantel during pregnancy should be reserved for those cases in which the parasite is causing clinical illness or public health problems.

Antibacterials: betalactam drugs, other antibacterials, antileprosy drugs, antituberculosis drugs, antifungal drugs and antiviral drugs (antiherpes and antiretroviral)

Tetracycline

Tetracycline is contraindicated during pregnancy. This broad spectrum antibiotic crosses the placenta, chelates calcium and is deposited in the developing teeth and bones of the fetus. The effects on bone are minimal, but discoloration of the teeth and enamel hypoplasia can occur from the end of the first trimester. Staining of the permanent teeth is most likely when tetracyclines are administered after 24 weeks' gestation.

Ciprofloxacin

Quinolone treatment in developing adolescents of several animal species is associated with acute arthropathy of the weight-bearing joints. A recent study examining the effect of intrauterine exposure to quinolones suggested that the use of ciprofloxacin during the first trimester of pregnancy is not associated with an increased risk of fetal malformations or musculoskeletal problems. Long-term follow-up is required to exclude subtle cartilage and bone damage.

Aminoglycosides

Except for eighth cranial nerve damage, no reports of congenital defects caused by streptomycin have been found. The Collaborative Perinatal Project[6] monitored 50,282 mother-child pairs, 135 of whom had first trimester exposure to streptomycin. For use any time during pregnancy, 355 exposures were recorded. In neither group was evidence found to suggest a relationship to large categories of major or minor malformations or to individual defects. Aminoglycoside antibiotics have no detectable teratogenic risk for structural defects. The study also concluded that the risk of deafness after *in utero* aminoglycoside exposure was small. Streptomycin is compatible with breastfeeding.

Chloramphenicol

Chloramphenicol should be avoided in late pregnancy and during labor because of the potential for the 'gray baby syndrome' in newborns. The syndrome usually starts 2–9 days after therapy is begun and causes vomiting, suck refusal, rapid irregular respiration, abdominal distension followed by flaccidity, an ashen gray color and hypothermia. About 40% of affected neonates die of circulatory collapse on or about the 5th day. Its use in pregnancy should be confined to life-threatening conditions, when no alternative is available.

Nitrofurantoin

Nitrofurantoin may be administered in pregnancy, but should be avoided near term. Low

levels of glutathione may predispose the fetus to hemolytic anemia if it is exposed to nitrofurantoin shortly before birth.

Vancomycin

Vancomycin is a bactericidal antibiotic with a fetal ototoxic effect. It acts mainly by inhibiting cell wall synthesis and inhibiting RNA synthesis in bacterial cytoplasmic membranes. It should be avoided unless benefit outweighs potential risk.

Trimethoprim

Trimethoprim inhibits the reduction of dihydrofolate to tetrahydrofolate and readily crosses the placenta appearing in measurable amounts in fetal blood. The use of trimethoprim in pregnancy was associated with an approximate quadrupling of the risk of cardiovascular defects and/or an oral cleft. Risk was increased with use during the second and third months after the last menstrual period but not before or after this time. It is advisable to avoid trimethoprim in the first trimester unless benefit outweighs potential risk, and administration, if prescribed, must always be accompanied with folic acid.

Antifungal drugs

Griseofulvin

Griseofulvin is a systemic agent used to treat fungal infections of the skin, hair and nails. It is a known teratogen in laboratory animals and crosses the human placenta. Griseofulvin use is contraindicated during pregnancy, and pregnancy should be avoided for 1 month after treatment. Men should not try to father children within 6 months of treatment.

Ketoconazole

Ketoconazole is used in systemic mycoses, serious chronic resistant mucocutaneous candidiasis, gastrointestinal mycoses, chronic resistant vaginal candidiasis and resistant dermatophyte infections of skin or fingernails. It inhibits placental microsomal aromatase and cytochrome P450. Although it has been used in some pregnant women without complications, it should be avoided during pregnancy as there is insufficient information to confirm its safety.

Antiprotozoal drugs: antiamebic and antimalarial drugs

Metronidazole

Most of the published evidence now suggests that metronidazole does not present a significant risk to the fetus. A possible small risk for cleft lip with or without palate abnormalities has been reported, but the validity and the clinical significance of this finding is questionable. Metronidazole is contraindicated during the first trimester in patients with trichomoniasis or bacterial vaginosis[9]. The American College of Obstetricians and Gynecologists (ACOG) recommends that clindamycin (orally or intravaginally) be used during the first trimester for symptomatic bacterial vaginosis[9]. The use of metronidazole for trichomoniasis or vaginosis during the second and third trimesters is acceptable, as either a single 2-g oral dose or a 7-day course of 750–1000 mg/day in divided doses. For other indications, metronidazole can be used during pregnancy if no other alternatives with established safety profiles are available. In these cases, the patient should be counseled about the potential risks and informed consent obtained before initiating therapy.

Chloroquine

A 1985 report[10] summarized the results of 169 infants exposed *in utero* to 300 mg of chloroquine base once weekly throughout pregnancy. The control group consisted of 454 non-exposed infants. Two study group infants had anomalies (tetralogy of Fallot and congenital hypothyroidism) compared with four in the control group. Based on these data, the authors concluded that chloroquine is not a major teratogen, but a small increase in birth defects could not be excluded. The amount of chloroquine excreted into milk is not considered to be harmful to a nursing infant.

Quinine

Newer agents have effectively replaced quinine to treat malaria. Although no increased teratogenic risk can be documented, its use during pregnancy should be avoided. Quinine is compatible with breastfeeding.

Antituberculous drugs

Rifampicin

No controlled studies have linked the use of rifampicin with congenital defects. Several reviews[11–13] have evaluated the available agents for treatment of tuberculosis during pregnancy. All concluded that rifampicin was not a proven teratogen and recommended use of the drug with isoniazid and ethambutol if necessary. The American Academy of Pediatrics[14] considers rifampicin to be compatible with breastfeeding.

Ethambutol

No congenital defects are linked to ethambutol. The literature[13,15,16] supports the safety of ethambutol in combination with isoniazid and rifampicin during pregnancy. Ethambutol is compatible with breastfeeding.

ADRENOCORTICAL STEROIDS

The adrenal cortex synthesizes two classes of steroids: the corticosteroids (glucocorticoids and mineralocorticoids) having 21 carbon atoms and the androgens which have 19. Cortisone is the main glucocorticoid, and aldosterone is the main mineralocorticoid. Glucocorticoids are administered in multiple formulations for disorders that share an inflammatory or immunological basis. Except in patients receiving replacement therapy for adrenal insufficiency, glucocorticoids are neither specific nor curative, but rather are considered palliative because of their anti-inflammatory and immunosuppressive actions.

Prednisolone is the biologically active form of prednisone. The placenta can oxidize prednisolone to inactive prednisone or even less active cortisone. A study of 229,101 patients exposed to prednisolone, prednisone and methyl-prednisolone during the first trimester failed to show any association between these agents and congenital defects[17]. When prednisolone was used throughout the pregnancy, cataracts in the newborn occurred in rare instances. At maternal doses of 20 mg, the infant would be exposed to minimal amounts of steroid. At higher doses, however, mothers are advised to wait at least 4 hours after a dose before nursing their infants.

Betamethasone use for therapy of preterm labor is associated with decreases in respiratory distress syndrome, periventricular leukomalacia and intraventricular hemorrhage in preterm infants. However, this drug can precipitate myasthenic crisis in patients with myasthenia gravis, induce hyperglycemia and rarely a hypertensive crisis. Single courses of betamethasone have no effects on the fetus, but multiple courses have been associated

with lower birth weights and reduced head circumference at birth[18–20]. Follow-up studies have not shown any differences in cognitive and pscychosocial development when compared with controls[21–23]. Hydrocortisone and its inactive precursor cortisone present small risks to the human fetus. These corticosteroids produce dose-related teratogenic and toxic effects in genetically susceptible experimental animals, which consist of cleft palate, cataracts, spontaneous abortion, IUGR and polycystic kidney disease.

Although extensive data[24,25] support no adverse effects in the vast majority of human pregnancies, adverse outcomes have been observed and may have been caused by corticosteroids. Moreover, the decrease in birth weight and a small increase in the incidence of cleft lip with or without cleft palate are supported by large epidemiologic studies. Because benefits of corticosteroids far outweigh fetal risks, these agents should not be withheld if the mother's condition necessitates their use. The mother, however, should be informed of the risks, so she can actively participate in the decision regarding whether to use these agents during her pregnancy.

IMMUNOSUPPRESSIVE DRUGS

Azathioprine

Azathioprine is a 6-mercaptopurine derivative which acts as a 'steroid-sparing' agent, suppressing cell-mediated hypersensitivity and altering antibody production. Use of azathioprine in pregnant patients with renal transplant, systemic lupus erythematosus and inflammatory bowel disease is extensive. Current evidence indicates that maternal use of azathioprine is not associated with an increased risk of impaired fetal immunity, growth retardation and prematurity. In children followed for up to 20 years, no increase in congenital abnormalities or subsequent problems such as childhood malignancy has been noted. The information on breastfeeding while taking azathioprine is without consensus. Despite little or no drug being found in breast milk, most rheumatologists advise avoidance of azathioprine if possible, or counsel against breastfeeding because of theoretical risks of immune suppression of the neonate.

Cyclosporine

Based on relatively small numbers, the use of cyclosporine during pregnancy apparently does not pose a major risk to the fetus. No pattern of defects has emerged in the few newborns with anomalies. Skeletal defects, other than a single case of osseous malformation, have not been observed. The disease process *per se* for which cyclosporine is indicated makes these pregnancies high risk and subject to numerous potential problems, of which the most common is growth retardation, and this is probably more closely related to the mother's disease rather than to her drug therapy. Nonetheless, a contribution from cyclosporine and corticosteroids cannot be excluded. Cyclosporine is contraindicated during breastfeeding due to its potential for immune suppression and neutropenia, unknown effect on growth, and possible association with carcinogenesis.

CYTOTOXIC DRUGS

These drugs exert their effects mainly on rapidly dividing cells, and hence are most dangerous at the stage of organogenesis. The alkylating agents cyclophosphamide and chlorambucil, and the folic acid antagonist methotrexate all are teratogenic and all are contraindicated in pregnancy. The risk of congenital abnormalities in cyclophosphamide-exposed children ranges between 16 and 22%, but its use may be contemplated later in pregnancy if the mother's disease is life threatening. Methotrexate should be discontinued at least 3 months prior to conception and folic acid (5 mg) supplementation given preconceptionally[10].

CARDIOVASCULAR DRUGS

Antiangina drugs

Nitroglycerin

The use of nitroglycerin during pregnancy does not appear to present a risk to the fetus. However, the number of women treated during pregnancy is limited, especially during the first trimester. With the smaller doses reported, transient decreases in the mother's blood pressure may occur, but these do not appear to be sufficient to jeopardize placental perfusion. Nitroglycerin appears to be a safe, effective, rapid-onset, short-acting tocolytic agent. The use of transdermal nitroglycerin patches is also effective when longer periods of tocolysis are required.

Antiarrhythmic drugs

Amiodarone

Amiodarone is an iodine-rich antiarrhythmic drug with proven benefit in the treatment of patients with ventricular and atrial arrhythmias. It can reach the fetus by transplacental passage and induce fetal hypothyroidism. It inhibits the conversion of thyroxine to triiodothyronine in most tissues. It may also inhibit thyroid hormone synthesis and secretion, causing hypothyroidism in 5–25% of patients[26]. Transplacental exposure to amiodarone may be associated with neurotoxicty. When compared with controls, amiodarone-exposed toddlers showed expressive language skills relatively poorer than their verbal skills[27]. One amiodarone-exposed toddler exhibited global developmental delay. Amiodarone-exposed older children had well developed social competence, favorable global IQ scores but exhibited problems with reading comprehension, written language and arithmetic, a picture reminiscent of the non-verbal learning disability syndrome[28]. In another report, normal psychomotor development was observed in two patients with full-scale IQ score, and verbal and performance IQ scores within normal range. However, these data need validation by larger studies. In conclusion, drug therapy of cardiovascular rhythm disorders should be avoided during the first trimester of pregnancy if possible, and drugs with the longest record of safety should be used as first-line therapy. Conservative therapies should be used when appropriate.

Digoxin

Of 229,101 completed pregnancies studied between 1985 and 1992, 34 newborns were exposed to digoxin during the first trimester[17]. One (2.9%) major birth defect was observed (one expected), an oral cleft. Although the number of exposures is small, these data are supportive of previous experience for a lack of association between the drug and congenital defects. Digoxin is compatible with breastfeeding.

ANTIHYPERTENSIVE DRUGS

Beta-adrenergic antagonists

Beta-adrenergic antagonists have fewer side-effects than most antihypertensives, but their safety in pregnancy is not so well established. Some studies found no adverse effects on the outcome of pregnancy, while others described a variety of fetal and neonatal complications[29]. The major concern is that if these drugs are used before 28 weeks' gestation, they may increase the risk of IUGR. Later complications

include bradycardia, hypotension, hypoglycemia and respiratory distress. However, many studies suggest that they are safe antihypertensives for use in the third trimester. If treatment of hypertension is required before 28 weeks, methyldopa should be the first drug of choice.

Angiotensin converting enzyme inhibitors

This group of drugs are orally active inhibitors of angiotensin converting enzyme, which is responsible for conversion of inactive angiotensin I to the potent pressor peptide angiotensin II. These drugs have been associated with prolonged renal failure and hypotension in the newborn[30], decreased skull ossification, hypocalvaria and renal tubular dysgenesis. In addition, there are several case reports of IUGR, oligohydramnios, patent ductus arteriosus and neonatal hypotension. The use of these drugs in the first trimester is not thought to produce structural malformations, so it is acceptable to cease treatment early in pregnancy and not necessarily preconception.

Loop diuretics (furosemide)

There is an association between use of furosemide in the first trimester and hypospadias. Furosemide is considered safe in breastfeeding. Its use is not recommended in the treatment of pre-eclampsia due to intravascular volume depletion.

Thiazide diuretics

Use of thiazides and related diuretics in the first trimester does not indicate that these agents are teratogenic. However, the Collaborative Perinatal Project[6] found an increased risk of defects when diuretics were used during the first trimester in women with cardiovascular disorders, but causal relationships cannot be inferred from these data without independent confirmation. Bendroflumethiazide, chlorthalidone, chlorothiazide and hydrochlorothiazide are compatible with breastfeeding

Spironolactone is a competitive antagonist of aldosterone at receptor sites in the distal renal tubules, causing a moderate salt and water diuresis with reduced loss of potassium and hydrogen. Spironolactone also exhibits antiandrogenic effects, probably through competitive inhibition at the level of testosterone, dihydrotestosterone and androstenedione receptors. These properties underlie its successful use in the treatment of idiopathic hirsutism. These antiandrogenic effects were observed in spironolocatone-exposed male animal fetuses born with anomalies of external genitalia[31]. Its use in pregnancy is contraindicated, and if diuretics are necessary another agent is preferable. It is also used for the treatment of hyperaldosteronism, where amiloride or potassium supplements may be alternatives in pregnancy.

ANTITHROMBOTIC DRUGS

Warfarin

Warfarin is a form of coumarin with vitamin K antagonist action. Its use in pregnancy is associated with a high incidence of fetal loss, congenital malformations and physical disability. Exposure to the drug between the 6th and 9th weeks of gestation is associated with defective ossification of bone resulting in nasal hypoplasia and chondrodysplasia punctata. On a molecular level, vitamin K inhibitors may alter calcium binding for several proteins, affecting bone ossification and causing the characteristic bony abnormalities of the 'fetal warfarin' syndrome. The syndrome constitutes skeletal defects (nasal hypoplasia and stippled epiphyses), limb hypoplasia (particularly distal digits), low birth weight (<10th centile), hearing loss and ophthalmic anomalies. The use of warfarin in the second and third trimester is associated with serious complications, mainly central nervous system abnormalities thought to be due to brain microhemorrhages. The defects include dorsal midline dysplasia (agenesis of corpus callosum and Dandy-Walker malformations) or ventral midline dysplasia (optic atrophy), mental retardation, delayed development, seizures and microcephaly. The risk of teratogenicity with warfarin led to the recommendation that heparin be substituted for the treatment and prophylaxis of venous thromboembolism. However, heparin is not as effective as warfarin in preventing arterial thromboembolism in women with artificial heart valves or mitral disease with arterial fibrillation. In these situations, the risk of thrombosis may exceed the risks of warfarin use, and warfarin therefore may be indicated. It should, however, be used with great caution and close monitoring of both the mother and fetus.

Heparin

Heparin is the anticoagulant of choice from the fetal perspective, as it does not cross the placenta. Two major side-effects that can occur with heparin treatment are heparin-induced thrombocytopenia and osteoporosis. Two types of thrombocytopenia occur with heparin treatment. Non-immune heparin-associated thrombocytopenia is associated with a mild reduction in platelet counts and occurs 2–5 days after heparin injection. Immune thrombocytopenia, on the other hand, occurs due to IgG antiplatelet antibodies, occurring 3–4 weeks after therapy and increasing the risk of thrombus formation.

LIPID-LOWERING AGENTS

Simvastatin

Based on the animal data and limited human experience, exposure to simvastatin during early pregnancy does not appear to present a significant fetal risk. The outcomes reported are within those expected in a non-exposed population. However, because the interruption of cholesterol-lowering therapy during pregnancy should have no apparent effect on the long-term treatment of hyperlipidemia, simvastatin should not be used during pregnancy. Women taking this agent before conception should ideally stop the therapy before becoming pregnant and certainly on recognition of pregnancy. Accidental use of the drug during gestation, though, apparently has no known consequences for the fetus. Because of the potential for adverse effects in the nursing infant, the drug should not be used during lactation.

HORMONES AND OTHER ENDOCRINE DRUGS AND CONTRACEPTIVES

Androgens

Danazol

Danazol is a testosterone derivative and a weak androgen, used for the treatment of endometriosis, menstrual disturbances, immune thrombocytopenic purpura, classic hemophilia, Christmas disease and α1 antitrypsin deficiency. Reports suggest virilization of the external genitalia of female fetuses exposed to the drug during pregnancy producing fused labia and clitoral hypertrophy[32]. It should be avoided in pregnancy.

Hormonal contraceptives

Because oral contraceptives are primarily combination products, it is difficult to separate entirely the fetal effects of the contained progestogens and estrogens. Except for the modified development of sexual organs, no firm evidence has appeared that establishes a causal

relationship between oral contraceptives and various congenital anomalies. The acronym VACTERL (vertebral, anal, cardiac, tracheal, esophageal, renal or radial, and limb) was used initially to describe fetal malformations produced by oral contraceptives or the related hormonal pregnancy test preparations (no longer available in the US). The Population Council[33] estimates that, even if the study findings for VACTERL malformations are accurate, such abnormalities occur in only 0.07% of pregnancies exposed to oral contraceptives. Some later reviewers[34] have concluded that the risk to the fetus for non-genital malformations after *in utero* exposure to these agents is small, if indeed it exists at all.

In contrast, the effect of estrogens and some synthetic progestogens on the development of the sexual organs is well established. Masculinization of the female infant has been associated with norethindrone, norethynodrel, hydroxyprogesterone, medroxyprogesterone and diethylstilbestrol. The incidence of masculinization of female infants exposed to synthetic progestogens is approximately 0.3%. Pseudohermaphroditism in the male infant is not a problem, because of the low doses of estrogen employed in oral contraceptives.

Progestogens

Although many of the progestagens used as contraceptive agents, such as norethisterone and levonorgestrel, are 19-nortestosterone derivatives and have mild androgenic properties with a potential to produce virilization of a female fetus[35], they are unlikely to do so owing to the small amounts present.

INSULIN AND OTHER ANTIDIABETIC AGENTS

Metformin may be beneficial for decreasing the incidence of fetal and/or newborn morbidity and mortality in developing countries where the proper use of insulin is problematic, as insulin is still the treatment of choice for this disease. Moreover, insulin, unlike metformin, does not cross the placenta and, thus, eliminates the additional concern that the drug therapy itself is adversely affecting the fetus. Carefully prescribed insulin therapy provides better control of the mother's blood glucose, thereby preventing fetal and neonatal complications. High maternal glucose levels, as may occur in un- or poorly treated diabetes mellitus, are closely associated with a number of maternal and fetal adverse effects, including fetal structural anomalies if the hyperglycemia occurs early in gestation. To prevent this, most experts, including ACOG, recommend that insulin be used for types I and II diabetes occurring during pregnancy and, if diet therapy alone is not successful, for gestational diabetes.

THYROID HORMONE AND OTHER ANTITHYROID DRUGS

Propylthiouracil

Of 229,101 completed pregnancies between 1985 and 1992, 35 newborns were exposed to propylthiouracil (PTU) during the first trimester[17]. One (2.9%) major birth defect was observed (one expected), a case of hypospadias (none expected). A 1992 study reported the retrospective evaluation of hyperthyroid pregnancy outcomes treated with either PTU ($n = 99$) or methimazole ($n = 36$)[36]. Three (3.0%) defects were observed in those exposed to PTU (ventricular septal defect, pulmonary stenosis, patent ductus arteriosus in a term infant), whereas one newborn (2.8%) had a defect (inguinal hernia) in the methimazole group. No scalp defects were observed. In comparison with other antithyroid drugs, PTU is considered the drug of choice for the medical treatment of hyperthyroidism during pregnancy, and is compatible with breastfeeding[37].

Methimazole and carbimazole

A specific pattern of rare congenital malformations secondary to exposure to methimazole during the first 7 weeks of gestation is reported that consists of some or all of the following: scalp or patchy hair defects; choanal atresia; esophageal atresia with tracheoesophageal fistula; minor facial anomalies; hypoplastic or absent nipples; and psychomotor delay. These defects may indicate a phenotype for methimazole embryopathy. Because of the possible association with aplasia cutis and other malformations, and the passage of methimazole into breast milk, PTU is the drug of choice for the medical treatment of hyperthyroidism during pregnancy. Both methimazole and carbimazole are compatible with breastfeeding.

PSYCHOTHERAPEUTIC DRUGS

Antipsychotic drugs

Lithium

Lithium carbonate may be administered to pregnant women for treatment of the manic phase in manic–depressive psychosis (bipolar disorder). The precise mechanism of action is unknown, but it is thought to be due to altered ion transport or inhibition of adenyl cyclase, influencing nerve excitation, synaptic transmission and neuronal metabolism in the CNS. Lithium is associated with an increased incidence of fetal abnormalities. Since the 1960s an international Register of Lithium Babies has collected information about lithium-exposed children in the first trimester of pregnancy[38]. It is estimated that 7.8% of lithium-exposed embryos develop abnormalities. Early data showed that the cardiovascular system is the most affected, with Ebstein anomaly affecting one-third of lithium-exposed embryos. While initial information regarding the teratogenic risk of lithium treatment was derived from biased retrospective reports, more recent epidemiological data indicate that the teratogenic risk of first trimester lithium exposure is lower than previously suggested. The clinical management of women with bipolar disorder who have childbearing potential should be modified using this revised risk estimate. If lithium is used for prophylaxis, it is advisable to discontinue it during the first trimester, unless its withdrawal would jeopardize the woman or her pregnancy. During pregnancy, the smallest dose possible for acceptable therapeutic effects should be used. Frequent small dosages avoid larger fluctuations in maternal plasma concentrations, and each dosage should not exceed 300 mg with even spacing throughout the 24-hour period. Plasma levels should be monitored every 3–7 days.

Drugs used in depressive disorders

Tricyclic antidepressants and fluoxetine

Tricyclic antidepressants and fluoxetine are the first-line choices in the management of depression. Tricyclic antidepressants have a long history of use without increasing teratogenic risk in pregnant women. Fluoxetine has been studied in prospective trials without evidence for a higher incidence of malformations or other teratogenicity. Doses of tricyclic antidepressants may need to be higher in pregnancy due to increased hepatic metabolism. Where appropriate, to avoid withdrawal symptoms in the neonate, antidepressants should be slowly withdrawn or reduced to the minimum dose prior to delivery.

Drugs used in generalized anxiety and sleep disorders

Benzodiazepines are contraindicated in the first trimester. Diazepam and its metabolite, desmethyl diazepam, freely cross the placenta

and accumulate in the fetal circulation with newborn levels about 1–3 times greater than maternal serum levels. Transfer across the placenta occurs as early as 6 weeks' gestation, suggesting that diazepam accumulates in the fetal circulation and tissues during organogenesis. In 1427 malformed newborns compared to 3001 controls, first trimester use of tranquilizers (diazepam most common) was associated with inguinal hernia, cardiac defects and pyloric stenosis[39]. Second trimester exposure was associated with hemangiomas and cardiac and circulatory defects.

The effects of benzodiazepines, including diazepam, on the human embryo and fetus are controversial. However, the risk appears to be low, if indeed diazepam and the other agents do cause birth defects. Continuous use during gestation results in neonatal withdrawal and a dose-related syndrome is apparent if diazepam is used close to delivery. Consequently, if the maternal condition requires the use of diazepam during pregnancy, the lowest possible dose should be prescribed. Abrupt discontinuation of benzodiazepines should be avoided, as severe maternal withdrawal symptoms (physical and psychological) may occur. Fetal withdrawal, such as that observed with narcotics, has not been reported, but should be considered.

Use during labor is considered safe as long as the dose does not exceed more than 30–40 mg and the drug is not used over a long period of time. Neonatal complications from benzodiazepines include floppy infant syndrome with hypotonia, lethargy, sucking difficulties or withdrawal syndrome with IUGR, tremors, irritability, hypertonicity, diarrhea/vomiting and vigorous sucking.

DRUGS ACTING ON THE RESPIRATORY TRACT

Theophyllines

The Collaborative Perinatal Project[6] monitored 193 mother-child pairs with first trimester exposure to theophylline or aminophylline. No evidence was found for an association with malformations. Theophylline withdrawal in a newborn exposed throughout gestation has been reported. Apneic spells developed at 28 hours after delivery and became progressively worse over the next 4 days[40]. Therapy with theophylline resolved the spells. Except for the precaution that theophylline may cause irritability in the nursing infant, the American Academy of Pediatrics[14] considers the drug to be compatible with breastfeeding.

RADIOACTIVE IODINE

Radioactive iodine therapy is contraindicated in pregnancy since the uptake by fetal thyroid results in thyroid ablation and hypothyroidism. Pregnancy should be avoided for at least 4 months after treatment with radioactive iodine therapy and investigations using ^{131}I in view of the theoretical risk of chromosomal damage and genetic abnormalities.

VITAMINS

Retinoids

Acitretin and isotretinoin

Acitretin and isotretinoin are synthetic vitamin A derivatives. Acitretin, a metabolite of etretinate, is an oral preparation used for the treatment of severe resistant or complicated psoriasis and some of the congenital disorders of keratinization. Isotretinoin reduces sebum secretion and in its oral form is used for the treatment of nodulo-cystic and conglobate acne and severe antibiotic-resistant acne. Teratogenic effects have been reported to occur in up to 25% of babies born to mothers who took retinoids. The embryopathy includes CNS defects (hydrocephalus, optic nerve blindness, retinal defects, micropthalmia, posterior fossa defects, and cortical and cerebellar

defects), craniofacial defects (microtia or anotia, low-set ears, hypertelorism, depressed nasal bridge, microcephaly, micrognathia and agenesis or stenosis of external ear canals), cardiovascular defects (transposition of great vessels, tetralogy of Fallot and ventricular or atrial septal defects), thymic defects (ectopia and hypoplasia or aplasia) and miscellaneous defects (limb reduction, decreased muscle tone, spontaneous miscarriage and behavioral abnormalities). Isotretinoin is eliminated from the body within 4 weeks of stopping treatment, but acitretin is eliminated more slowly and pregnancy should be avoided for 2 years after a course of the drug. Fetal abnormalities have not been associated with topical retinoids, but it is advisable to avoid their use in pregnancy and ensure women use adequate contraception.

VACCINES IN PREGNANCY

Live attenuated vaccines are generally avoided in pregnancy. All killed vaccines are safe in pregnancy. Vaccines that give passive immunization are safe in the preconception period and during pregnancy. A list of vaccines and their use is shown in Table 4.

CONCLUSION

Current practice of prescribing in the preconceptional period is similar to that in patients who are not planning for a pregnancy. With the limitations in the available data regarding safety; however, the possibility of serious detrimental effects to the fetus, many of which may not be even identified in the fetal

Table 4 Usage of vaccines in pregnancy and preconception. (Adapted from the CDC guideline[41])

Hepatitis A	The safety of hepatitis A vaccination during pregnancy has not been determined; however, because hepatitis A vaccine is produced from inactivated (hepatitis A virus), the theoretical risk to the developing fetus is expected to be low. The risk associated with vaccination should be weighed against the risk for hepatitis A in pregnant women who may be at high risk for exposure to hepatitis A virus
Hepatitis B	Pregnancy is not a contraindication to vaccination. Limited data indicate no apparent risk for adverse events to developing fetuses when hepatitis B vaccine is administered to pregnant women. Current vaccines contain non-infectious HBsAg and should cause no risk to the fetus.
	Pregnant women who are identified as being at risk for HBV infection during pregnancy (e.g. having more than one sex partner during the previous 6 months, been evaluated or treated for a sexually transmitted disease, recent or current injection drug use, or having had an HBsAg-positive sex partner) should be vaccinated
Human papillomavirus (HPV)	Quadrivalent HPV vaccine is not recommended for use in pregnancy.
	If a woman is found to be pregnant after initiating the vaccination series, the remainder of the three-dose regimen should be delayed until after completion of the pregnancy. If a vaccine dose has been administered during pregnancy, no intervention is needed
Influenza (inactivated)	Vaccination with inactivated influenza vaccine is recommended for persons who are at increased risk for severe complications from influenza, such as women who will be pregnant during the influenza season
Influenza (LAIV)	Should not be used in pregnancy

continued

Table 4 *continued*

MMR	Measles-mumps-rubella (MMR) vaccine and its component vaccines should not be administered to women known to be pregnant. Because a risk to the fetus from administration of these live virus vaccines cannot be excluded for theoretical reasons, women should be counseled to avoid becoming pregnant for 28 days after vaccination with measles or mumps vaccines or MMR or other rubella-containing vaccines If vaccination of an unknowingly pregnant woman occurs or if she becomes pregnant within 4 weeks after MMR vaccination, she should be counseled about the theoretical basis of concern for the fetus; however, MMR vaccination during pregnancy should not be regarded as a reason to terminate pregnancy
Pneumococcal (PPV23)	The safety of pneumococcal polysaccharide vaccine during the first trimester of pregnancy has not been evaluated, although no adverse consequences have been reported among newborns whose mothers were inadvertently vaccinated during pregnancy
Polio (IPV)	Although no adverse effects of IPV have been documented among pregnant women or their fetuses, vaccination of pregnant women should be avoided on theoretical grounds. However, if a pregnant woman is at increased risk for infection and requires immediate protection against polio, IPV can be administered in accordance with the recommended schedules for adults
Rubella	Rubella-susceptible women who are not vaccinated because they state they are or may be pregnant should be counseled about the potential risk for congenital rubella syndrome and the importance of being vaccinated as soon as they are no longer pregnant
Tetanus, diphtheria and pertussis (Tdap)	Pregnancy is not a contraindication for use of Tdap. Data on safety, immunogenicity and the outcomes of pregnancy are not available for pregnant women who receive Tdap. When Tdap is administered during pregnancy, transplacental maternal antibodies might protect the infant against pertussis in early life. They also could interfere with the infant's immune response to infant doses of TdaP, and leave the infant less well protected against pertussis
Varicella	The effects of the varicella virus vaccine on the fetus are unknown; therefore, pregnant women should not be vaccinated. Non-pregnant women who are vaccinated should avoid becoming pregnant for 1 month following each injection. For susceptible persons, having a pregnant household member is not a contraindication to vaccination. If vaccination of an unknowingly pregnant woman occurs or if she becomes pregnant within 4 weeks after varicella vaccination, she should be counseled about the theoretical basis of concern for the fetus; however, varicella vaccination during pregnancy should not be regarded as a reason to terminate pregnancy
BCG	Although no harmful effects to the fetus have been associated with BCG vaccine, its use is not recommended during pregnancy

continued

Table 4 *continued*

Japanese encephalitis (JE)	No specific information is available on the safety of JE vaccine in pregnancy. Vaccination poses an unknown but theoretical risk to the developing fetus, and the vaccine should not be routinely administered during pregnancy. Pregnant women who must travel to an area where risk of JE is high should be vaccinated when the theoretical risks of immunization are outweighed by the risk of infection to the mother and developing fetus
Rabies	Because of the potential consequences of inadequately treated rabies exposure, and because there is no indication that fetal abnormalities have been associated with rabies vaccination, pregnancy is not considered a contraindication to postexposure prophylaxis. If the risk of exposure to rabies is substantial, pre-exposure prophylaxis might also be indicated during pregnancy
Typhoid	No data have been reported on the use of any of the three typhoid vaccines among pregnant women
Yellow fever	The safety of yellow fever vaccination during pregnancy has not been established, and the vaccine should be administered only if travel to an endemic area is unavoidable and if an increased risk for exposure exists. Infection of the fetus with YF17D apparently occurs at a low rate and has not been associated with congenital anomalies. If international travel requirements are the only reason to vaccinate a pregnant woman, rather than an increased risk of infection, efforts should be made to obtain a waiver letter from the traveler's physician. Pregnant women who must travel to areas where the risk of yellow fever is high should be vaccinated and, despite the apparent safety of this vaccine, infants born to these women should be monitored closely for evidence of congenital infection and other possible adverse effects resulting from yellow fever vaccination
Zoster (singles)	Contraindications: Zostavax should not be administered to individuals who are or may be pregnant. It is not known whether Zostavax can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, naturally occurring VZV infection is known to sometimes cause fetal harm. Therefore, Zostavax should not be administered to pregnant females; furthermore, pregnancy should be avoided for 3 months following vaccination

life, emphasizes the need for change of practice. In view of the above-mentioned as well as unforeseen dangers, prescribing in the preconceptional period should in the future be on the same grounds as prescribing for pregnancy.

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SECTION 6

Gynecological and surgical conditions

24

Prior cervical conization and uterine sparing cervical cancer surgery

Imran Hamzawala and Charlotte Chaliha

INTRODUCTION

Cancer of the cervix is the second most common female cancer, with more than half a million cases occurring annually worldwide. Approximately 30% of women with cervical carcinoma are less than 35 years of age and, for many of these women, fertility is a major issue[1]. Cervical screening programs have significantly reduced the incidence and death rates due to cervical cancer in developed countries with a concomitant increased rate of detection of early cervical cancer accompanied by a peak incidence of preinvasive disease (cervical intraepithelial neoplasia (CIN)) at around 30 years of age[2]. Thus, women may present earlier in reproductive life with issues regarding fertility and future pregnancy which could be compromised depending on the treatment offered. Whilst the benefits of cervical screening are regularly cited, it has not been implemented worldwide, and deficiencies are particularly apparent in resource poor nations.

Large loop excision of the transformation zone is presently the standard treatment of precancerous cervical changes in those areas of the world where such technology is available. Cervical conization is often used for superficially invasive or microinvasive carcinoma of the cervix (FIGO stage 1A1) in women wanting to preserve fertility as the risk of parametrial extension and lymph node metastasis in stage 1A1 carcinoma of the cervix is less than 1%[3]. FIGO stage 1A2 tumors have a 7.8% incidence of nodal metastases, whereas this increases to 16–18% with FIGO stage 1B tumors[4]. The traditional treatment of cervical cancer is either radical hysterectomy or radiotherapy to the pelvis, both of which inevitably compromise fertility[5]. The obvious impact on fertility of traditional surgery has led to the introduction of techniques to preserve uterine function such as the radical trachelectomy. However, in order to offer fertility sparing surgery, patients must be carefully selected by specific examination under anesthetic and careful review of available histology obtained from previous biopsies. A magnetic resonance imaging (MRI) scan should be performed for careful assessment of cervical and paracervical tissues to exclude more aggressive extension of disease in order to accurately stage the tumor[6,7].

Both the treatment of CIN and early stage cervical cancer with uterine sparing surgery may have an impact on fertility and pregnancy outcomes, and all patients seeking a fertility sparing procedure must be counseled with regards to potential oncologic and obstetric outcomes. This chapter discusses the current fertility sparing procedures and their effect on future fertility and pregnancy.

RADICAL TRACHELECTOMY

Radical trachelectomy can be performed either vaginally or abdominally depending on the surgeon's preference and level of expertise. In a vaginal trachelectomy, the cervix is removed along with parametrial tissue and a cuff of vagina by the vaginal route with a simultaneous laparoscopic pelvic lymphadenectomy[8,9]. The uterine body is left intact and a non-absorbable suture, acting as a cervical cerclage is placed around the uterine isthmus to maintain uterine competency for future pregnancies. Abdominal radical trachelectomy is essentially a similar procedure, albeit involving an abdominal approach. Postoperative morbidity with trachelectomy includes dysmenorrhea (24%), dysplastic Pap smears (24%), irregular or intermenstrual bleeding (17%), problems with cervical sutures (14%), excessive vaginal discharge (14%), isthmic stenosis (10%), amenorrhea (7%) and deep dyspareunia[10]. Posttrachelectomy, in the absence of adverse prognostic factors, patients are advised to use contraception for 6 months before they consider pregnancy to ensure that no oncological concerns are present prior to a pregnancy[11]. If prognostic factors such as positive lymph nodes and involved histologic margins are present, these warrant completion of treatment in the form of radical hysterectomy or chemo/radiotherapy. Such additional therapy should be undertaken at a suitable postoperative time which is usually 4–6 weeks postoperation[12]. All trachelectomy cases require close gynecological oncology follow-up at 3 monthly intervals for the first year, 4 monthly intervals for the second year, 6 monthly intervals until 5 years and then yearly until 10 years. After 10 years, if no evidence of recurrence is present, patients should be able to return to the 3 yearly screening program or a similar program that is acceptable to the requisite bodies of different nations[12]. Consideration of pregnancy during this follow-up period should be in liaison with a gynecological oncologist for advice and follow-up during and after pregnancy.

Oncologic prognosis of trachelectomy procedures

Radical vaginal trachelectomy

A total of 790 patients have reportedly undergone radical vaginal trachelectomy in published studies which noted 4% recurrences and 2% deaths from these recurrences[13]. These results are comparable to those of radical hysterectomies for similar sized lesions[14]. With a tumor size of less than 20 mm and a depth of invasion of less than 10 mm, the incidence of parametrial involvement is 0.6%[15]. Hence, radical vaginal trachelectomy is reserved for women with tumors less than 20 mm in diameter and with invasion of less than 10 mm[16].

Dursun *et al*. in their critical literature review of radical vaginal trachelectomies reported the median age as 31 years and median follow-up time of 48 months (1–176 months). Some 60% of patients had a diagnosis of squamous cell carcinoma and 40% had adenocarcinoma. The overall recurrence rate was reported as 4.2% and the death rate as 2.8%[17].

Radical abdominal trachelectomy

Some 116 patients have undergone radical abdominal trachelectomy in published studies worldwide which also report two recurrences[13]. Ungar *et al.* reported the largest series of 33 patients with a mean age of 30.5 years (25–37 years) who underwent radical abdominal trachelectomy. During follow-up (median 47 months), no recurrences were observed. These authors suggest that the radical nature of the parametrial, sacrouterine, vesciocervical and pelvic lymphatic tissue resection with the abdominal approach may contribute to high levels of disease free survival rates[18].

Fertility and pregnancy outcomes postradical trachelectomy

Radical trachelectomy offers hope of future fertility; however, posttrachelectomy, patients express distress and significant concerns regarding conception and pregnancy lasting for up to 6 months[19]. Apart from the physical recovery from an operative intervention, the uncertainty of conception and the acknowledgment of the potential for a high-risk pregnancy are obvious concerns for these patients. Accordingly, the immediate months postsurgery represent an ideal time for readdressing potential concerns (stenosis, sexual function, reproduction) and providing referrals for further support if needed[20]. The use of vaginal dilator therapy and vaginal moisturizers is extremely beneficial in addressing vaginal stenosis, scarring and/or dyspareunia following cancer treatment[21]. These modalities also could be beneficial in treating trachelectomy patients with the above symptoms. Stretching of tissues due to dilator therapy may reduce fibrosis and scarring if initiated early on and may beneficially improve oxygenated blood flow to the requisite tissues[22]. The complexity of aftercare, which may vary greatly from patient to patient, is markedly enhanced by the addition of a nurse specialist and mental health professional to the multidisciplinary team looking after trachelectomy patients.

Fertility and miscarriage

In their summary of fertility data on patients who had undergone radical trachelectomy (six series), Plante *et al.* reported an overall fertility rate of 13% (40 of 310 patients). In this group, 14 conceived with reproductive assistance, as the adjusted fertility rate was 8% (26 of 310 patients). It was also noted that patients with infertility secondary to cervical causes or ovulatory dysfunction had a reasonable chance of conceiving with assisted reproductive techniques such as *in vitro* fertlization (IVF) or intrauterine insemination (IUI). However, patients with infertility secondary to male factor, uterine factor or unexplained factors were less likely to conceive[23]. Existing data on radical trachelectomy suggest factors such as cervical stenosis or adhesion formation may cause subfertility[15,23 24,], as is also the case when lack of cervical mucus, subclinical salpingitis and subclinical chronic endometritis are present[24–26].

Given the above circumstances, it is important to assess prior medical issues that may adversely impact future fertility. Ideally, collaborations with fertility specialists should be developed for optimal counseling and management[23]. Boss *et al*., reviewing the literature, which included 16 studies involving 355 radical trachelectomy patients, noted that 43% of patients had attempted pregnancy and that 70% conceived. In those who became pregnant, 21% had a first trimester miscarriage, 8% had a second trimester miscarriage, 21% delivered in the third trimester before 36 weeks, whereas only 50% delivered after 36 weeks[27]. In a further series, Plante *et al*. reported a series of 50 pregnancies in 31 patients (retrospective review of 72 patients treated from October 1991 to October 2003) following fertility preserving vaginal radical trachelectomy. In this study, the rate of first trimester miscarriages was similar to that of the general population (16%), as was the rate of second trimester miscarriage (4% vs 3–5%). In their series, 72% were able to carry their pregnancies to the third trimester and, of these, 78% reached term (>37 weeks). The preterm delivery rate was higher than in the general population (16% vs 12%)[23].

Chorioamnionitis and premature rupture of membranes

The increased risk of preterm delivery may be related to premature rupture of membranes

secondary to chorioamnionitis as reported in several series. In the series reported by Schlearth *et al*. in 2003, one pregnancy ended at 22 weeks with chorioamnionitis and another ended at 26 weeks with fetal death[28]. In another series reported by Shepherd *et al*., six of the seven preterm births were preceded by spontaneous rupture of membranes without contractions[24]. This is similar to a series by Bernardini *et al*. where spontaneous rupture of membranes occurred without contractions in four of the six premature deliveries. Expectant management was carried out and all four women delivered within 4 days, three showing signs of infection at the time of delivery[25].

The etiology of premature rupture of membranes is thought to be either mechanical or infectious and most probably a combination of both[24,25,29]. Shepherd *et al*. suggested that the permanent cerclage placed around the isthmus at the time of radical trachelectomy, even though buried under vaginal mucosa, may still act as a source of bacterial contamination[24]. Kolomainen *et al*. reported a case of a postvaginal radical trachelectomy in a woman whose Pap smear showed presence of *Actinomyces*. Since *Actinomyces* have been associated with chorioamnionitis resulting in preterm labor, the authors recommended that anaerobic cultures be done on pregnant patients after a radical trachelectomy either as a routine or if signs of premature labor develop[30].

The cervical mucus plug may function to protect against ascending vaginal infection. In patients who undergo radical trachelectomy, however, disruption of endocervical glands results in inevitable reduction of mucus secretion. Thus impaired or absent production of mucus can facilitate the access of micro-organisms to the choriodecidual space and uterine cavity. Decidual cells, resident macrophages of decidua and neutrophils initiate a cytokine response. This elevation of cytokines is considered to be a cause of preterm labor and the subsequent occurrence of preterm premature rupture of membranes[31,32]. Accordingly, little benefit may derive from being conservative with trachelectomy patients who present with premature rupture of membranes, as they are likely to deliver within 2–3 days and a delay may lead to serious neonatal and maternal infection complications[23]. However, it has been suggested in one study that expectant management is a reasonable option until 32–34 weeks of pregnancy in patients with premature rupture of membranes without signs of chorioamnionitis[33].

Management of miscarriage

If first trimester miscarriage occurs, expectant management or induction with misoprostol is generally successful. If necessary a dilatation and curettage can be performed under a general anesthetic but cervical dilatation should be kept to a minimum to reduce the risk of breaking the cerclage around the isthmus[23].

The management of second trimester loss is more difficult. In the series by Plante *et al*. two patients spontaneously miscarried at 17 and 20 weeks, respectively[34]. In the series of Bernardini *et al*. the patient with second trimester loss delivered after removal of cerclage and induction with misoprostol[25]. Hysterotomies should be reserved for patients who fail the expectant/medical management or show signs of sepsis.

Antenatal care

Due to the increased risk of cervical incompetence, these patients need to be followed more frequently. A visit in a high-risk obstetric clinic every 2 weeks is recommended from 18 to 28 weeks and weekly thereafter. If cervical incompetence is diagnosed, placement of another cervical cerclage around the uterine isthmus should probably be attempted, depending on the stage of pregnancy[11].

Obstetricians caring for women who have undergone radical trachelectomy should be familiar with the procedure and aware of potential complications. If possible, a high-risk consultant with expertise in management of cervical incompetence and preterm labor should take the lead in managing these women.

Obstetricians should also stringently aim to reduce the risk of introducing infections. Hence, digital examinations should be reduced to a minimum and cervical cytology should probably be avoided beyond the first trimester[23]. Cessation of coitus is advisable between 20 and 36 weeks of pregnancy[35]. Cervical length may be followed up by serial vaginal ultrasounds[36]. This procedure has been used in non-trachelectomy patients where transvaginal ultrasound is found to be a good predictor of cervical incompetence with a good negative and poor positive predictive value[37].

Although, serial fetal fibronectin has been suggested for use in the third trimester to predict preterm birth, no data exist with regards to its use in trachelectomy patients[38,39]. Extrapolating from the data on premature birth in the general population, progesterone suppositories could be considered in pregnant women posttrachelectomy as they appear to significantly reduce preterm birth secondary to cervical incompetence in high-risk populations such as women with prophylactic cerclage and women with previous preterm birth[40–42].

Routine prophylactic steroids to accelerate fetal lung maturity are recommended in view of risk of premature delivery[24,25].

For patients with recurrent miscarriages a Saling technique was described in 1981. This is performed by excising and undermining the vaginal mucosa near the cervical opening, stretching it over the cervix and resuturing it in place to completely cover the cervical os to prevent ascending infection. It is usually performed at 14 weeks of gestation and patency of the cervical opening is restored at the time of cesarean section[43].

Mode of delivery

In view of the permanent cerclage placed at radical trachelectomy, delivery by cesarean section is indicated. In general, cesarean sections after radical trachelectomy are performed via a classical incision in order to prevent extension of the wound[44]. Generally 37–38 weeks is considered an optimal time for elective delivery[13].

Postnatal follow-up

No data suggest that pregnancy affects the cancer prognosis. Following delivery, the patient is advised to follow-up with her routine oncology appointments.

CONIZATION SURGERY

Factors affecting treatment of CIN include size and site of lesion, severity on colposcopic examination or histology of previous biopsy, anatomical characteristics of the transformation zone and suspicion of glandular neoplasia or microinvasive disease[45]. Two types of treatment are used for management of preinvasive disease: excisional and ablative procedures. Excisional procedures include cold knife conization, large loop excision of the transformation zone and laser conization. Ablative procedures include laser ablation, cryotherapy and diathermy.

Ablation in general is used to treat smaller, superficial and less severe areas. Excision treatment is used when there is a suspicion of invasion, a larger area, or transformation zone deep in the endocervical canal. Hence a larger area of cervix will be removed with excisional treatment. Studies show that treated women remain at higher risk than the general population for developing subsequent invasive cervical cancer, even many years after treatment[46–48].

Pregnancy outcome after conization surgery

A meta-analysis of 27 studies executed by Kyrgiou *et al*. in 2006 evaluated pregnancy outcomes in women previously treated for CIN. This pooled analysis reported that the risk of preterm delivery amongst women with large loop excision of transformation zone or cold knife conization was 1.7 and 2.6 times higher, respectively, than that of untreated women. A significantly increased risk was also noted for low birth weights with both methods, for premature rupture of membranes after large loop excision of the transformation zone and for cesarean delivery after cold knife conization. Laser ablation was not associated with adverse obstetric outcomes[49].

In a recent meta-analysis, Arbyn *et al*. looked at severe obstetric or neonatal outcome in women treated for CIN with excisional procedures (cold knife conization, large loop excision of transformation zone) and ablative procedures (laser ablation, cryotherapy and diathermy). Criteria for severe obstetric and neonatal outcome included perinatal mortality, severe (<32/34 weeks) and extreme (<28/30 weeks) preterm delivery, and severe low birth weight (<2000 g, <1500 g and <1000 g)[50]. This meta-analysis showed that cold knife conization was associated with severe adverse pregnancy outcomes, which included increased risk of perinatal mortality, severe preterm delivery and extreme low birth weight infants. The meta-analysis by Kyrgiou *et al*. in 2006 had previously suggested an increased risk of preterm delivery and low birth weight babies was associated with large loop excision of the transformation zone, but in the more recent meta-analysis large loop excision of the transformation zone did not significantly affect the more serious adverse obstetric outcomes; however, it was also suggested that it cannot be considered as completely free of adverse pregnancy outcome. Both meta-analyses showed that ablation with laser had no effect on pregnancy outcomes.

Laser conization may increase the risk of preterm delivery[51] and outcome after conization may be influenced by cone size and height[52,53], with women whose cone height is greater than 10 mm having a higher rate of preterm delivery than those with a cone height of less than 10 mm[54]. Inevitably the knife excises more tissue than the loop. Loop excisions that remove large amounts of cervical tissue probably have the same effect as knife cone biopsies. Most loop excisions in young women with fully visible transformation zone need to be only 1 cm deep and this conservatism should protect against serious obstetric outcomes[50].

Transvaginal ultrasound scan can predict preterm birth in women who have had large loop excision of the transformation zone procedures. The negative predictive value of the ultrasound scan is 95.2% for spontaneous preterm birth at less than 37 weeks in women with large loop excision of transformation zone[55]. Hence, this may be a valuable tool in pregnancy management along with serial scans for fetal growth in view of the increased risk of low birth weight babies.

Mode of delivery after conization

Vaginal delivery is not contraindicated after excisional procedures on the cervix. Paraskevaidis *et al*. looked at delivery outcomes after loop electrosurgical excision procedures for microinvasive cervical cancer. Their study showed that treated women did not have more delivery complications compared with controls, apart from a shorter duration of labor[56]. Another study by Klaritsch *et al*. looked at delivery outcomes after cold knife conization of the cervix and showed that cold knife conization is a risk factor for preterm birth and premature rupture of membranes and seems to be a risk factor for cervical tears; however, no difference was noted in mode of delivery, duration of labor, chorioamnionitis and use of oxytocin[57]. In contrast, an increased risk of cesarean section after cold knife excision was reported by Kyrgiou *et al*.[49].

CONCLUSION

Cervical cancer is a disease that often affects women in their reproductive years. This is important, as with recent delays in childbearing in many developed countries, women may not have started their families when a diagnosis is made. Issues regarding fertility and conception therefore are highly important to them and have prompted a move from the very radical procedures of the past to fertility sparing procedures.

Treatments such as conization of the cervix and radical trachelectomy have shown promise with regards to future fertility and pregnancy; however, they are not without complications including premature rupture of membranes and preterm labor, both of which may lead to significant neonatal concerns and physical and emotional distress for the mother. Hence, patients undergoing radical trachelectomy/conization, need to be thoroughly counseled regarding issues of fertility sparing surgery on prognosis of disease, fertility and pregnancy. It is also important to note that these patients need to be managed in an obstetric department with a high-risk obstetrics consultant specialized in looking after such patients. Multidisciplinary input is essential with involvement of gynecological oncologist, neonatologist, nurse specialist and mental health professional.

Ultraconservative fertility sparing surgery for very early invasive cervical cancer (1A2 and early 1B1) is now under consideration. This involves a simple trachelectomy or a large cold knife cone with laparoscopic pelvic lymphadenectomy. However, the concept of an ultraconservative treatment approach warrants further investigation to evaluate the oncological safety and long-term prognosis[34]. Human papilloma virus (HPV) testing may help with the follow-up of women after treatment for CIN. Due to its high negative predictive value, it can clearly identify those women who are at a low risk of residual or recurrent disease[58–60]. This may give more confidence to clinicians to resort to less aggressive treatment practises. The introduction of HPV vaccine may also decrease the incidence of cervical cancer and precancerous lesions requiring treatment, which may subsequently reduce adverse obstetric outcomes.

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25
Benign conditions of the genital tract

Christopher B-Lynch

VAGINAL MALFORMATION

A number of vaginal malformations have been described. The vagina may be inaccessible because of an intact hymen. It also can be malformed by a transverse (horizontal) or vertical (longitudinal) septum. In the presence of a transverse septum, menstrual blood may not pass freely and a hematocolpos may also be present. Vaginal examination should easily identify the obstruction, and hematocolpos can be detected either by the presence of a tense fullness behind the septum, or with the aid of an ultrasound examination which will further delineate its extent and whether the uterus is itself dilated with further menstrual fluid collection. A cruciate incision under general anesthesia is generally all that is required to correct this abnormality. A partial or subseptum can be high or low in the vagina. The lower it is the better is the prognosis for pregnancy, and complete excision can be achieved. Excision can also be achieved by using a CO_2 laser. This results in very little surgical trauma and minimal scar tissue is created. The prognosis for pregnancy is good for a low septum and much reduced for a high septum.

A vertical (longitudinal) septum may be present in variable lengths up to a complete separation of the vagina creating two cavities. This can occur as either a high or low septum or a complete partition of the vagina. There have been instances where normal vaginal delivery has occurred alongside a longitudinal septum through one of the compartments. If such a defect is detected before pregnancy, a CO_2 laser excision or other appropriate surgical treatment can remove the septum and facilitate creation of a normal functioning vagina. It is usual for women who are preconceptional to complain if they have this condition, because they experience difficulty in inserting a tampon or dyspareunia when attempting to have normal vaginal intercourse. The treatment results are usually excellent.

Vaginal atresia

The vagina develops from the cloacae and is usually covered with squamous epithelium. Because of its proximity to the anus, which develops from the same epithelial anlagae, similar malformations to those of the anal canal may occur. Vaginal atresia may be associated with an absence of rudimentary development of the uterus known as the Rokitansky syndrome, most commonly presenting at puberty with amenorrhea or cryptomenorrhea in the presence of normal secondary sexual characteristics. If the use of regular vaginal dilators fails, then a variety of surgical techniques performed in collaboration with a plastic surgeon could be beneficial.

If the uterus is underdeveloped and has failed to connect with the vagina then surrogacy would seriously have to be considered as a childbearing option.

UTERINE MALFORMATION

A variety of uterine malformations have been described varying from a unicornuate uterus (Figure 1) to complete division or duplication of the uterus, commonly described as a double uterus with two horns separated in its low end, along with two tubes and two ovaries[1]. These patients are usually asymptomatic but may present with fertility problems, recurrent miscarriage, scanty menstruation and painful or heavy periods. They are susceptible to preterm labor and abnormal presentation of the fetus. An ultrasound scan can identify the condition well before pregnancy.

A unicornuate uterus has a high miscarriage and premature labor rate which may lead to anything from extreme prematurity to late prematurity and immature development of the fetus. It is commonly acknowledged that if a unicornuate uterus has carried a pregnancy to term the prognosis is good for subsequent pregnancies.

The well known Strassman's operation, which involves incision at the uterine fundus from one horn to the other transversely and then re-suturing anteriorly and posteriorly to create a larger cavity, theoretically may enable the patient to carry a pregnancy to a more advanced gestation. Though such corrective surgery can be performed, the benefit of successful and advanced pregnancy is by no means guaranteed. Some forms of bicornuate uterus may have a redundant horn or a dominant horn. If pregnancy occurs in the redundant horn, the chance of ectopic pregnancy or rupture of the uterus is higher. In some cases a redundant horn can obstruct the passage of the fetal head into the birth canal from the pregnancy that is in the dominant horn. Careful evaluation is important to understand the nature and extent of the problem well before pregnancy occurs.

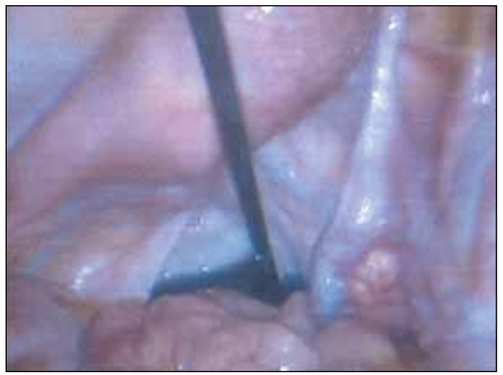

Figure 1 Patient aged 35. Unicornuate uterus with congenital absence of left tube and ovary. Copyright Mr C. B-Lynch 2009

When a septum is discovered within the uterine cavity, it is appropriate to remove it using a hysteroscopic approach, which is commonly followed by an immediate insertion of an intrauterine contraceptive device of the Mirena type for 6 weeks to minimize adhesion formation.

The numerous varieties of malformation make it imperative that during the course of investigating patients for infertility all clinicians undertake proper physical examination to exclude abnormalities of the genital tract[1].

GENITAL WARTS

Genital warts commonly present in young women, often before they become pregnant. The method of transmission is still unclear, although the causative viral agent is well known. The vast majority of cases are managed in the specialist genitourinary medical clinic; although in many countries management is in the hands of generalists or obstetricians/gynecologists. Some centers provide medication for self application at home with the inherent pitfalls in managing such a condition effectively (especially when the warts are extensive) by this protocol. Guidelines are available from von Krogh *et al*. and the Health Protection Agency[2,3].

In the UK about 71,000 new cases of genital warts are reported annually by genitourinary medicine clinics. A common association with *Chlamydia* infection is present. Women with these conditions experience local irritation of the vulva and vagina as well as marked anxiety. Human papillomavirus (HPV) is the cause of infection and has the associated risk of cervical cancer at a later date in some individuals, as HPV types 16 and 18 are found in most cases of cervical cancer. As such, the infection is a particularly relevant condition for discussion in terms of preconceptional medicine. Following initial diagnosis, the behavior in pregnancy is unpredictable. Often the pregnant state is associated with marked growth of the warts which, if not treated in a timely basis, can become problematic in terms of general comfort and, in some instances, locomotion. When neglected, obstruction of vaginal delivery is a possibility. It is probable that the immunosuppressive effect of pregnancy may opportunistically charge these viral eruptions to proliferate. Currently young adolescent women are offered immunization, but evidence of the long-term effectiveness of this program is awaited. Genital warts can be found anywhere around the tract of the female genitalia including the introitus, vulva, vagina and cervix[4].

Diagnosis

Most cases of genital warts are diagnosed by visual appearance with the individual lesions displaying characteristic warty heads. These are contagious and can be passed onto the male and vice versa. Collaboration with a dermatologist is often helpful, because the differential diagnosis includes uninfectious skin lesions including malignancies. It is essential not to confuse sexually transmitted diseases with other genital warts such as molluscum contagiosum which are flatter eruptions of the vulva and contain central cheesy material. Another consideration should be condyloma lata of secondary syphilis which are softer more fleshy lesions especially confined to the perianal region. Appropriate blood screening tests could differentiate these various diagnoses.

Treatment is not always necessary, as a proportion of these warty lesions resolve spontaneously[5]. However, many clinicians will treat all cases because it is not possible to distinguish those lesions which regress spontaneously.

Treatment

For mothers who are contemplating and planning a pregnancy it is prudent to treat visible lesions before becoming pregnant. No treatment modality can be guaranteed to be 100% effective and relapses can occur. Treatments such as podophyllin and imiquimod can be applied. Long-term toxicity (especially if lesions are large) may mean using an alternative such as podophyllotoxin. This is a cytotoxic agent with the active component of podophyllin. It is applied as a cream base and is effective in young women. Other treatments such as imiquimod, cryotherapy and trichloroacetic acid are recommended either in isolation or in combination[6].

In pregnancy warts tend to grow quite rapidly. Small warts can be treated conservatively; larger warts can be excised even in pregnancy. Cervical warts should be excised using the laser, and when warts are large and invading the vagina, serious consideration should be given to delivery of the baby by cesarean section. Transmission from mother to baby can occur if lesions are present in the vagina. Pediatric manifestations of genital wards include laryngeal polyps of the infant and toddler.

Treatment with podophyllotoxin should be avoided in pregnancy because of concerns regarding potential toxins. Urethral warts can be cauterized. In pregnancy, surgical removal of localized warts is recommended, but recurrence may occur after apparent surgical clearance.

Because the chances of greater proliferation of wart viral changes could be high in patients who are HIV positive and pregnant, these

individuals should be managed jointly between the sexually transmitted disease unit and the HIV consultant. It is also good practice to screen for other sexually transmitted diseases in patients who request HIV screening, regardless of whether they are pregnant at the time of the request.

Ideally, patients with genital warts should have annual cervical smears before becoming pregnant. Genital warts are rarely associated with oncogenic HPV infections. Transmission of genital warts can be controlled by the use of barrier methods of contraception such as the condom, which may prove valuable preventive measures against other HPVs[3].

Summary

Key points regarding genital warts include:

- The diagnosis of genital warts is usually a clinical one
- HPV 6 and 11, which are not associated with an increased risk of malignancy, are associated with 90% of wart infections
- Most patients can be treated at home with topical agents such as podophyllotoxin or imiquimod
- All treatments, including ablative treatment, have a relapse rate of around 30%
- Warts have a natural history and may regress spontaneously
- No treatment is always an option
- Screening for other sexually transmitted infections (STIs) should be routine for any patient presenting with genital warts
- Currently, vaccines are available to inoculate against HPV infections of malignant potential. Evidence of their long-term effectiveness is eagerly awaited.
- All wart virus infections have the capacity to grow in pregnancy when the immune response may be suppressed.

BENIGN TUMORS OF THE BARTHOLIN'S GLAND

The Bartholin's glands provide appropriate secretions following sexual stimulation to prevent or minimize friction during sexual intercourse.

From time to time, obstructions of the ductal aspect of the gland cause swelling, pain and/or edema of the gland or infection by bacterial tracking of the duct which causes inflammation of the gland leading to abscess, intense pain and fever. This organ is sometimes described as the greater vestibular gland in the lower third of the labia majora. Inflammatory changes can occur at any time before or during pregnancy, causing pain and discomfort along with fever or abscess formation. Active and urgent management is indicated.

Independent of the Bartholin's gland, superficial vulval cysts may or may not become secondarily infected. Most often, they are asymptomatic and require no treatment even in pregnancy other than to occasionally discharge a cheesy-like substance. In such instances, excision in conjunction with antibiotics of appropriate culture and sensitivity may be considered.

Changes in vulva pigmentation need advice regarding further management as 10% of pigmented lesions can become malignant melanomas. In pregnancy, pigmented lesions are particularly susceptible to further changes, and the pigmentation *per se* probably reflects the immunosuppressant effect of pregnancy.

VULVAL INTRAEPITHELIAL NEOPLASIA

Vulval intraepithelial neoplasia (VIN) is commonly a feature of squamous origin (Bowen's disease or Bowenoid papulosis), in which grading the severity of changes depends on clinical appearance as well as histology not unlike the grading of cervical intraepithelial neoplasia (CIN). The lesion might have a rough surface

and be flattened like vulval wart infection but can also appear with indistinct borders. Paget's disease can present with similar appearances to VIN. These are also uncommon and have demarcated borders, are very commonly multifocal, are eczematoid in character and are associated with 25% of adenocarcinoma within the pelvis, perianally or at distant sites. The recommended treatment is wide excision of the focal lesion in consultation with a colorectal surgeon preoperatively.

CERVICAL INTRAEPITHELIAL NEOPLASIA

Lesions of this type are premalignant conditions, and many women have had abnormal smears prior to pregnancy. The various classifications of such abnormalities include terms such as mild, moderate or severe dyskaryosis. These gradings mainly indicate changes in the cellular pattern from mild to severe in progression which signify high or low risk.

Liquid based cytology was recently introduced to achieve more robust detection of the presence of abnormal cells and their character. This process also enables the non-visible type of wart virus that may be present on the cervix to be identified and classified as to which group it belongs, including HPV 16 and 18 both of which have malignant potential.

Following an abnormal smear report, the patient should have a colposcopic examination. The biopsy taken at the time of this procedure will diagnose and classify the abnormality into a high or low risk category (CIN high or low grade)[7].

The impact of this procedure in pregnancy is now well recognized. Biopsy is commonly performed as a loop excision of the transformation zone (the boundary is where the glandular cells border the squamous cells). This border may harbor 95% of the abnormal cells of precancer or cancer origin. Some cervixes have a larger surface area of abnormality than others. The larger is the surface area of abnormality, the greater is the chance of scar tissue formation after the loop excision procedure. Sometimes the scarring is sufficient to interfere with conception and in other instances in the process of parturition. It is common to warn patients who have had loop excision surgery of these risks and for health care personnel to assess the cervix when patients are in labor and possibly explain any slow progress.

A cone biopsy is sometimes necessary for high grade colposcopic lesions. This operation, which removes the abnormal area along with normal tissue in a cone shaped specimen is usually performed under regional or general anesthesia, either as a cone loop excision or knife cone biopsy. Unfortunately, the cervix may be shortened or scarred significantly afterwards, and, in a worst case scenario, may lead to difficulty in passing menstrual blood and/or retention of menstrual blood in the uterine cavity (hematometra) along with considerable pain. This latter condition is relieved when the cervix is dilated to empty the uterus. It is important only to dilate the cervix to a reasonable diameter so as not to cause cervical incompetence or interfere with the integrity of subsequent pregnancy. Follow-up Papanicolau smear may become necessary even in the early part of pregnancy. Most other investigations, including follow-up smears after successful treatment, can be performed 3 months after the postnatal period.

MENORRHAGIA AND DYSMENORRHEA

The quantity and significance of heavy periods is usually difficult to assess[8,9]. The classical categorization of heavy periods describes approximately 40 ml with 70% loss in the first 48 hours in the healthy European population. As this is a subjective definition, the clinical impact of excessive bleeding is assessed based on the clinical features described by patient including tiredness, listlessness, pallor as well

as anemia when assessed by hemoglobin values[10]. Menorrhagia commonly leads to iron deficiency anemia. The impact of which is even more significant in the less developed world where a patient might attempt to accomplish the activities of daily living with hemoglobin levels at half the value of those of women in the western world.

Menorrhagia is one of the main reasons for seeking medical advice, and was a common indication for hysterectomy as late as the 1980s when about 40% of women having a hysterectomy listed this reason for seeking surgical therapy. In the UK, 1 in 5 women have their uterus removed by the age of 55, albeit with a significant proportion of the pathology reports showing a normal uterus, with dysfunctional uterine bleeding having been the principle cause of heavy periods[11].

The introduction of ablative therapy has reduced the incidence of hysterectomy dramatically since the 1990s[12]. Currently, surgical procedures such as hysterectomy are balanced against the potential associated mortality and morbidity risks of these operations versus the far lesser morbidity of the ablative regimens.

Most women with menorrhagia also complain of dysmenorrhea, particularly women in the fertile age group and where other causes of heavy periods have not been excluded such as fibroid uterus, endometriosis, pelvic inflammatory disease (PID) and malignant or premalignant conditions of the uterus. In a significant proportion of instances of dysmenorrhea, the character may be congestive or spasmodic, although usually with congestive dysmenorrhea pain appears before bleeding starts and promptly decreases in severity during the flow. In contrast, the spasmodic variety worsens with menstrual flow past the first day.

It is important to understand this difference, because women who have spasmodic dysmenorrhea may well have endometriosis or adenomyosis that needs early diagnosis and therapy. The presence of dysmenorrhea should alert the clinician to perform appropriate investigations and then to consider the consequence of these examinations on the patient's fertility potential. In this regard, preconceptional diagnosis not only determines the feasibility of pregnancy and its uneventful progress but also diagnoses conditions the treatment of which facilitates pregnancy[11].

Because endometriosis is a classic cause of spasmodic dysmenorrhea and dyspareunia, a diagnostic laparoscopy could reveal this early enough to enable appropriate treatment. Such investigations may also provide the opportunity to assess tubal and ovarian function characteristics (Figure 2).

UTERINE FIBROIDS

Fibroids are benign tumors the size and location of which are variable. As such they can be submucosal, intramural, subserosal, intracervical or pedunculated and in the broad ligament. Fibroids are well circumscribed, with a whorl type of soft tissue, appearing in approximately 20% of women of reproductive age, many of whom are asymptomatic.

They are extremely common in the Afro-Caribbean population where most women tolerate their symptoms remarkably well even

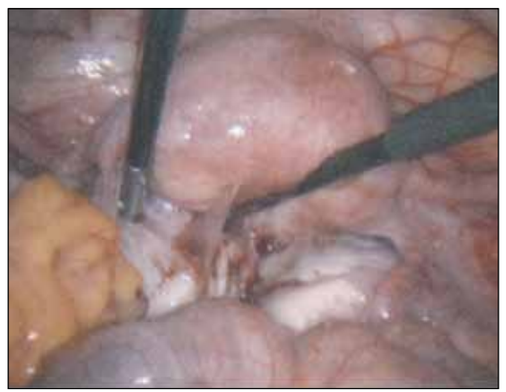

Figure 2 Patient aged 32. Bilateral ovarian endometriosis in pouch of Douglas (the kissing ovaries syndrome). Copyright Mr C. B-Lynch 2009

though they are often anemic. A significant proportion of patients with fibroid tumors are reluctant to have any form of surgical intervention.

The introduction of interventional radiology (embolization) has presented a new option for the management of fibroids. In 2004 the National Institute of Clinical Excellence (NICE) provided guidance for clinicians to consider uterine artery embolization for the treatment of fibroids, although it is important to note that currently no concrete data exist pertaining to the effectiveness or outcome of embolization procedures for treatment of fibroid tumors, including the preservation of fertility potential, or the reduction of potential fecundity in patients who wish to conceive. The NICE document comments on indications, means of performance of the procedure, ethics, safety and reduction in mean fibroid volume and blood loss[13]. Counseling and consenting of such women is essential for those who consider this alternative procedure in the management of fibroid uterus[1]. Uterine artery embolization should not be recommended without careful consideration in the treatment of symptomatic uterine fibroids, endometrial polyp or submucosal fibroid[1].

Women who have had the uterine cavity open during a prior myomectomy should be offered cesarean section when they become pregnant to minimize or avoid the risk of uterine rupture.

Conjunctive medical treatment

Medical treatment for fibroids and menorrhagia can be achieved by the use of mefenamic acid, tranexamic acid, non-steroidal anti-inflammatory drugs (NSAIDs) or antifibrinolytic agents. All are useful medical treatment for menorrhagia, but are not effective in every patient. Commonly in fibroid menorrhagia, one or another of these agents may control bleeding but not the pain. If the pain persists, the patient becomes reluctant to persevere with medical treatment.

The luteinizing hormone releasing hormone (LHRH) analogue (goserelin) is used to shrink fibroids and control bleeding by suppressing ovarian function, generally as pretreatment for myomectomy or prehysterectomy for very large fibroids. Decapeptyl 3 mg injection on a monthly basis for 6 months or goserelin 3.6 mg monthly by injection for the same duration are both acceptable. Patients administered either of these medications should be warned about the side-effect of premature chemical menopause and might need some adback treatment such as tibolone or low-dose estrogens to reduce the disturbing effect of estrogen withdrawal.

ENDOMETRIOSIS

The etiology of endometriosis is unknown. Common clinical features suggest ectopic deposits of endometrial tissue outside the uterine cavity itself or ectopic location within the myometrium *per se*, when the condition is termed adenomyosis. Apart from heavy menstruation, endometriosis is characteristically associated with severe dysmenorrhea of the spasmodic type. The location of endometriosis is variable and can involve organs such as the bladder and rectum that lie within the pouch of Douglas[11] (Figure 2) or involving one or both ovaries either superficially or within its depth.

Foci of endometriosis can also be found in distant organs such as the appendix, bowel, diaphragm or pulmonary area. Regarding fertility potential, it is essential to ascertain that the tubes are not involved. If the ovaries are involved, appropriate treatment should be administered to facilitate pregnancy where indicated (Figures 3 and 4). A significant number of patients with endometriosis become pregnant spontaneously and their symptoms characteristically resolve whilst they are no

longer menstruating. This is not to say that they are cured, but their symptoms abate markedly, although there is no evidence to show that pregnancy cures endometriosis.

Patients with endometriosis commonly complain of deep dyspareunia because of the position of the uterus, as endometriosis within the pouch of Douglas commonly causes uterine retroversion and fixation. If endometriosis involves the rectum and lower bowel, patients can complain of painful defecation and inefficient bowel emptying (Figures 5–8). Endometriosis is a significant problem for women, especially those in the fertile age group where its presence not only causes classic menorrhagia and dysmenorrhea but also sexual problems. In extreme cases, pelvic endometriosis can require bowel resection with bypass or diversion surgery, or, in cases of ureteric involvement, bypass or diverted urinary tract surgery.

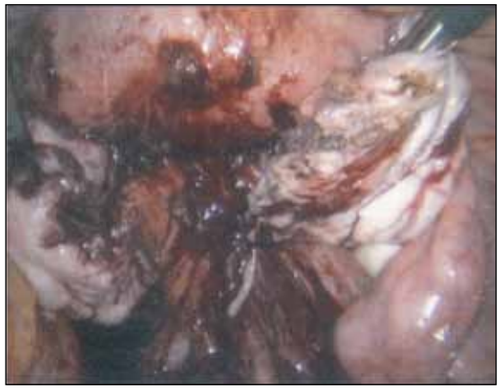

Figure 3 Patient aged 32. Surgical marsupialization, irrigation and drainage, followed by goserelin medical treatment. Copyright Mr C. B-Lynch 2009

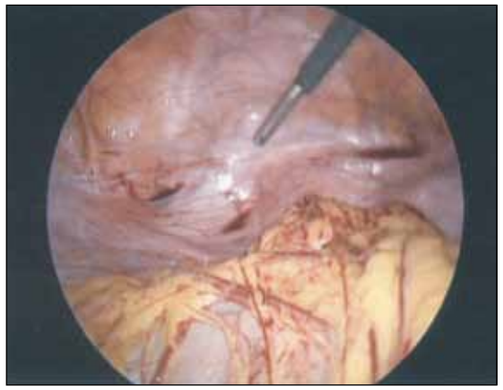

Figure 5 Patient aged 30. Severe uterine retroversion and retroflexion. Copyright Mr C. B-Lynch 2009

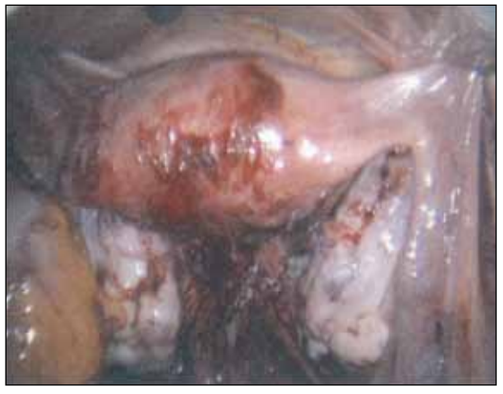

Figure 4 Patient aged 32. Surgical treatment result. Uneventful pregnancy 6 months later with normal delivery. Copyright Mr C. B-Lynch 2009

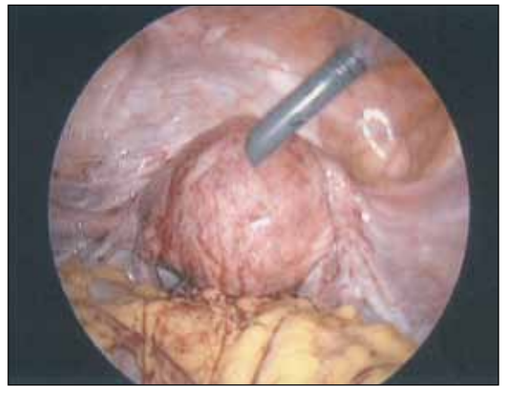

Figure 6 Patient aged 30. Vaginal manipulation of uterus to test for successful laparoscopic uterine ventrosuspension. Copyright Mr C. B-Lynch 2009

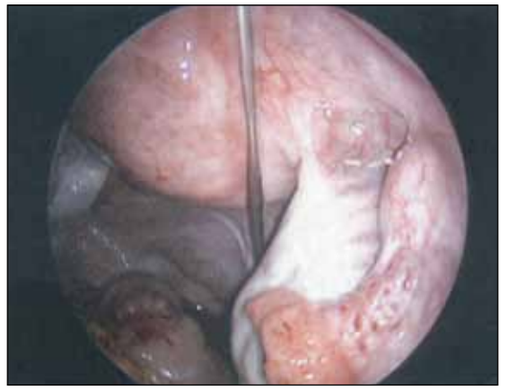

Figure 7 Patient aged 30. Right round ligament lift and fixation. Copyright Mr C. B-Lynch 2009

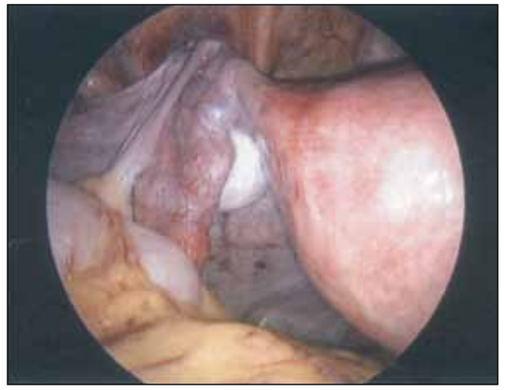

Figure 8 Patient aged 30. Left round ligament lift and fixation for relief of deep dyspareunia. Uneventful pregnancy and normal delivery following laparoscopic ventrosuspension. Copyright Mr C. B-Lynch 2009

It is important to manage the clinical features of endometriosis and properly investigate these patients, offering medical treatment first. Patients with endometriosis should undergo laparoscopy, at which time lesions can be classified as having pink (early inflammatory changes), chocolate (established) or white (resolving) characteristics. Patients' symptoms often do not correlate with the laparoscopic severity of endometriosis. Treatment must be individualized taking the entire clinical picture into account. Quality of life and fertility potential are crucial in the management of this condition. When the bowel is involved, it is mandatory that a colorectal surgeon forms part of a multidisciplinary team management (Figures 3 and 4).

Clinical features should be comprehensive. Deep infiltrating nodular lesions are best palpated during menstruation. Transvaginal scan may have a role in the diagnosis of the disease involving the bladder or rectum but is of limited value. Magnetic resonance imaging (MRI) can be superior to ultrasound scan but not of greater benefit compared to laparoscopy. The chemical marker CA125 may be elevated in endometriosis, but its elevation is not always diagnostic of the condition.

Women who want to avoid hormonal therapy to treat their pain should consider NSAIDs. Assisted reproduction should be considered to improve fertility chances in minimal to mild endometriosis. *In vitro* fertilization (IVF) is an appropriate treatment for endometriosis especially when tubal function is compromised.

Laparoscopic ovarian cystectomy is recommended for endometriotic cysts greater than 4 cm in diameter. Surgical treatment for endometriomas is often useful before IVF, although women should be counseled regarding the risk of reduced ovarian function after surgery.

Treatment with gonadotropin releasing hormone (GnRH) 3–6 months before IVF in women with endometriosis often increases the rate of clinical pregnancy. Finally, it is worth noting that patient self help groups can provide invaluable counseling support and advice.

PELVIC PAIN

Pelvic pain in women may or may not be associated with significant pathology. Many

women who experience pelvic pain outside the normal menstrual cycle have conditions that may affect their fertility such as PID, adhesions or pelvic cysts. PID in premenopausal women and particularly pre-pregnancy women may result from bacterial infection or STI. The end point is usually described as terminal hydrosalpinges with flimsy pelvic adhesions. The collection of inflammatory material at the resolution stage of gonorrhea and *Chlamydia* infections shows typical tubal distension, distortion, irregularity and thinning of the tubal wall, which may then progress to a chronic inflammatory form. Because hydrosalpinges can contain immune complexes resulting from the resolution process which can affect the IVF success rate, salpingectomy may improve the chance for success in patients who have had tubal disease prior to IVF treatment.

Infected products of conception from a miscarriage may cause proximal damage or occlusion of the tube commonly described as cornual blockage. Such patients have very little or no chance of conceiving even after tubal reconstructive surgery, and IVF remains the key management strategy. Diagnostic procedures (hysteroscopy and laparoscopy) are essential to exclude genital tract abnormality and to ascertain the exact site of chronic PID.

In the vagina itself, about 20% of women may have bacterial colonization, including group B streptococci and sometimes coliform bacteria, which ultimately may affect not only the prospect of IVF success but also pregnancy outcomes. Group B streptococci may cause premature rupture of the membranes and can affect the baby leading to serious neonatal morbidity. When group B streptococci are found colonizing the vagina in pregnancy the protocol of management should be multidisciplinary including a bacteriologist, pediatrician, obstetrician and neonatologist. It is because of the significant consequences of PID that all clinically diagnosed patients should be treated immediately to protect against any progression of this condition. The choice of antimicrobial or antibacterial therapy will be dependent on the clinical presentation and the need for singular or broad spectrum cover. It is not acceptable to delay medical treatment when PID is suspected or diagnosed.

All mothers should have counseling about the presence of such bacteria in the vagina as soon as the diagnosis is made in pregnancy. PID can cause a significant amount of pain, deep dyspareunia and distortion of the pelvic anatomy.

BENIGN PELVIC CYSTS

The most common cyst in young women of fertile age is the dermoid cyst. Dermoid cysts represent congenital cysts arising from the migration of the ovary from the mesenchymal ridge down to the pelvis assisted by the round ligament to its definitive position on the ovarian fossa. These ovaries may contain cells capable of a variety of tissue differentiation of no ovarian function. The cysts can be found incidentally on ultrasound scan or computed tomography (CT) evaluation. Whenever large cysts are discovered these should be removed by laparoscopy or open surgery as appropriate, as torsion is always possible and can result in destruction of viable ovarian tissue and considerable morbidity.

Dermoid tumors have a very low chance, about 10%, of malignant potential. Careful management of this condition should be discussed with the patient who wants to become pregnant.

Whereas it is acceptable to remove the cyst and conserve the ovary, there is never an absolute indication to remove the ovary because it contains a dermoid cyst. Clinical consideration must be given to the fertility status or preconception state of the patient and general clinical condition before oophorectomy is carried out for a dermoid cyst (Figures 9–12).

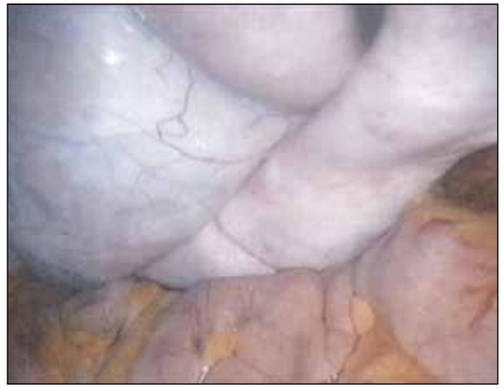

Figure 9 Patient aged 19. Presented with 35 cm left dermoid cyst. Laparoscopically deflated and aspirated. Copyright Mr C. B-Lynch 2009

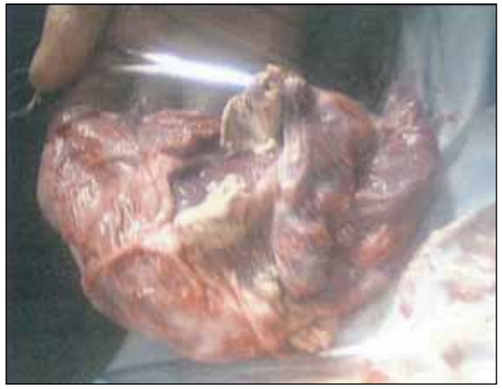

Figure 11 Patient aged 19. Dermoid cystectomy excised and confirmed histologically. Copyright Mr C. B-Lynch 2009

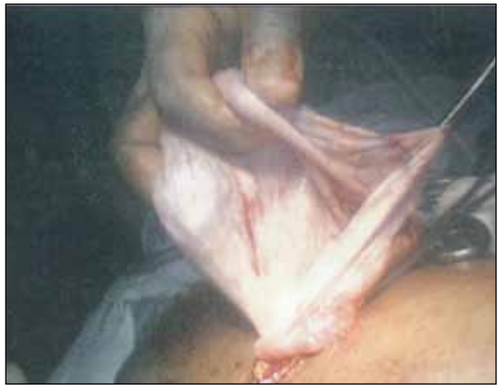

Figure 10 Patient aged 19. Cyst exteriorized and extracorporeal left ovarian cystectomy performed. Copyright Mr C. B-Lynch 2009

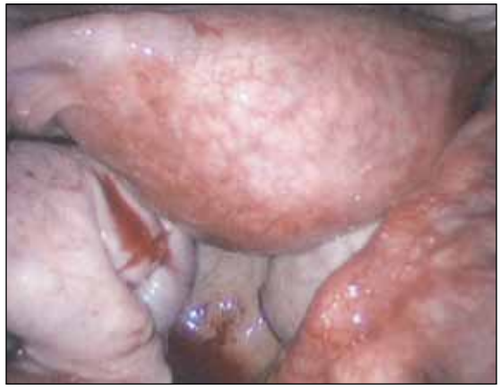

Figure 12 Patient aged 19. Replacement of left ovary into pelvis. Copyright Mr C. B-Lynch 2009

BENIGN OVARIAN CYSTS (UNILOCULAR CYSTS)

These conditions exist as benign serous cystadenomas or benign mucinous cystadenomas and are normally diagnosed after cystectomy when no other clinical indication of abnormality is present within the cyst. Preoperative assessment may include the CA125 marker test, which if elevated must be investigated by further high definition scan and other markers. Although there is a 10% chance of these cysts becoming malignant, the vast majority if properly evaluated require only laparoscopic surgery. It is well recognized that cysts can grow to an enormous size, often in the pre-pregnancy patient, and their excision necessitates skilful laparoscopy or laparotomy.

If all the markers are strongly suggestive of a benign condition, then removing the cyst while conserving ovarian tissue is appropriate and beneficial to the pre-pregnancy patient. To

do nothing is not an option, as it is well recognized that cysts can undergo torsion which would require prompt ovarian cystectomy.

SALPINGIAN CYSTS

These cysts are usually of moderate size and are commonly diagnosed as an incidental finding at routine laparoscopy. If they are tiny, they can be left alone. On the other hand, if they are of a size which might interfere with tubal function by way of torsion, they should be removed laparoscopically, first by deflating the cyst and then resecting the stalk. Occasionally postlaparotomy adhesions may present with loculated cystic formations within adhesion strands or bands which appear as ovarian cysts with the potential to have false imaging and mislead the clinician. Such cysts should be assessed carefully by CT or MRI scanning and interpreted by an interventional radiologist. It is safer to be conservative rather than to proceed to further laparotomy.

It is most essential to evaluate clinical cystic changes thoroughly before surgical intervention, as a proportion of cysts do not originate from a gynecological organ. Occasionally retroperitoneal cysts masquerade as pelvic cysts. Clinicians must always seek the advice of surgical colleagues when the diagnosis is in doubt and in the best interest of the patient.

POLYCYSTIC OVARIAN SYNDROME

Polycystic ovarian syndrome (PCOS) presents problems for the patient as well as her gynecologist. The historical background of this condition goes back to 1845 when Chereau first described the sclerotic changes of the ovaries. Almost a century later, in 1935, Stein and Leventhal[14] described the classical features of PCOS and proposed wedge resection of the ovary as treatment (Figure 13). In subsequent years, our understanding of the

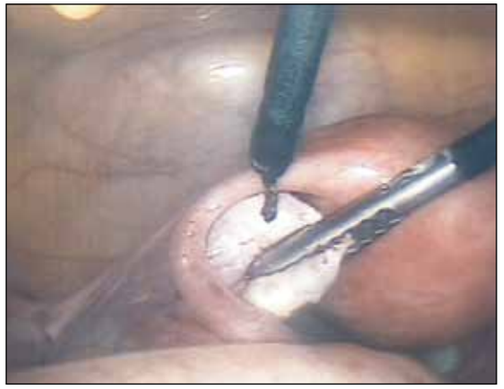

Figure 13 Patient aged 26. Drilling diathermy treatment. Copyright Mr C. B-Lynch 2009

pathophysiological basis of the condition has improved enormously and a variety of treatment options have been suggested with favorable results[15,16].

This condition, common among women of reproductive age, has generated much debate regarding its definition and diagnosis. Apart from chronic anovulation and oligomenorrhea, it causes fertility problems for a significant number of women with the diagnosis[17]. Normally, two categories of patients having this condition come to attention. On the one hand, there is the patient who presents with oligomenorrhea and is worried about the condition; on the other, there are patients who experience anovulation and are worried about fertility prospects.

In the former category, reassurance is probably all that is necessary. If medical treatment is required, metformin potentiates insulin activity and may correct the condition and facilitate a return of menstruation. Unfortunately, a significant number of these women do not respond to metformin in terms of restoration of ovulation. This medication, backed by clomiphene, may improve the prognosis for pregnancy, but not in all circumstances. Overcoming the insulin resistance by metformin is not the only pathological process warranting treatment to achieve fertility. A body

of evidence shows that insulin resistance is the principle underlying defect and treatment target. Such therapy may not only resolve the immediate clinical problem but also has the potential to reduce the risk of vascular disease in later life[17]. Another group of patents have hyperandrogenemia. These patients may also have hirsutism as a problem in addition to their fertility problems. Obesity is a recognized association.

Commonly three approaches are used in the management of PCOS in young women. The first is to treat the symptoms with antiandrogens for conditions such as hirsutism, then to use contraception for menstrual irregularities and finally to institute ovulation induction for the preconceptional patient who is actively seeking pregnancy. Induction of ovulation can be prompted medically or using ovarian diathermy with the laser or wedge resection.

Sinha and B-Lynch demonstrated successful ovulatory responses following the use of the YAG laser in the form of marsupialization of the ovary[16]. This technique was further supported by Aziz and B-Lynch with an equally good outcome[18] (Figure 14). These techniques found markedly reduced serum LH concentrations and normal menstrual cycles in 32 (91%) patients with successful ovulation confirmed by day 21 progesterone and 17 pregnancies out of 24 women wishing to get pregnant (71%). Eleven patients were treated for irregular cycles, hirsutism, premenstrual syndrome and/or pelvic pain. There was one miscarriage at 8 weeks, but nine pregnancies resulted in the birth of normal live babies.

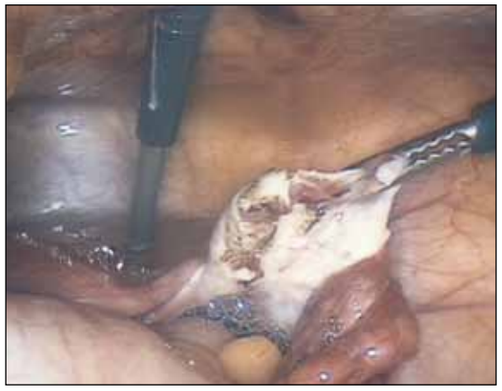

Figure 14 Patient aged 26. Stromal depth exposure. Histology confirmed polycystic ovary. Uneventful pregnancy and normal delivery 12 months later. Copyright Mr C. B-Lynch 2009

The conclusion of this small study was that clinicians should consider this effective laparoscopic surgical technique with ovarian drilling when medical treatment has failed to produce fertility. The paper of Sinha and B-Lynch[16] also showed a reduction in miscarriage rates. Women with PCOS achieving pregnancy might suffer from a short luteal phase for which progesterone therapy might be useful.

It is important to understand that women with PCOS do not all fail to get pregnant spontaneously. The condition can exist in a variety of forms, such as in one ovary but not the other, or in both ovaries. It is because of the bizarre nature of this condition that active management should be encouraged in women who seek to become pregnant and fail with medical treatment as a first line.

ACKNOWLEDGMENT

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26

Pregnancy and fertility counseling in breast cancer survivors

Christobel Saunders, Angela Ives and Toni Musiello

Breast cancer is the commonest malignancy in females, with nearly 1.5 million newly diagnosed cases worldwide each year. In developed countries, it affects up to 1 in 8 women in their lifetime. Whilst breast cancer is relatively uncommon in younger women, with only 15% of cases diagnosed in women less than 45 years, the prevalence of the disease results in large numbers of women of childbearing age being affected. The recent and growing trend in developed countries to delay childbearing is leading to an increase in the number of premenopausal women who have not started or completed their families at the time of diagnosis. Under these circumstances, younger women who are diagnosed with breast cancer have important but complex decisions to make, and these decisions relate not only to treatment but also to how it will affect their fertility, chance of pregnancy and contraceptive choices in the future. Previous research has shown that young women diagnosed with breast cancer want the opportunity to discuss and understand the consequences of the options open to them; however, studies find that fertility issues are not fully discussed or that information is lacking[1–3]. Even when information is available, women often do not feel adequately supported in making decisions.

Breast cancer treatment exerts a negative impact on fertility for several reasons: first, the toxic effects of chemotherapy on ovarian follicles reduce ovarian function and reserve; second, once chemotherapy treatment is completed, women are advised to delay attempting conception for 2 years, thus further reducing potential ovarian function; and third, when endocrine therapy is recommended for up to 5 years, ovarian function declines even further[4]. In addition, and most importantly, the knowledge of having a potentially life threatening illness and the associated psychosocial effects of a breast cancer diagnosis may color the decision a couple may make about future children. The negative impact of breast cancer treatment and its associated recommended delays in attempting conception mean that only 7% of premenopausal women remain fertile[5–8] and only 3–4% become pregnant following a diagnosis of breast cancer[9–11].

It is important to consider, however, that the reported low proportion of women who become pregnant after a diagnosis of breast cancer could result from under-reporting of pregnancy terminations and missed abortions in this population, as is the case in the general population. According to Barthelmes and Gateley, 14–44% of pregnancies conceived after a diagnosis of breast cancer are terminated[12]. These numbers suggest the actual percentage of women who conceive after a diagnosis of breast cancer may be far greater than previously appreciated.

The reasons women may choose to terminate a pregnancy subsequent to a diagnosis of breast cancer include fear that the

breast cancer will recur or that the cancer will affect their child. Many women successfully deliver a healthy child following a diagnosis of breast cancer, but still may fear the effects of the breast cancer on the child and/or the pregnancy on the cancer. Studies to date demonstrate that a subsequent pregnancy is not likely to affect the outcome of the breast cancer, and, equally, a prior diagnosis of breast cancer will not necessarily affect the pregnancy outcome[9–11,13]. Further prospective studies are needed, however, to explore how pregnancy and fertility affect a diagnosis of breast cancer and how the breast cancer may affect the offspring of women who conceive after diagnosis.

OUTCOMES AND SURVIVAL OF WOMEN WITH PRIOR BREAST CANCER WHO SUBSEQUENTLY CONCEIVE

Pregnancy is not usually recommended in the first 2 years following the treatment of breast cancer, as most early recurrences develop within this time[14,15]. This recommendation is not made because the pregnancy will affect breast cancer outcome. Rather, it is made to ensure that the woman does not become pregnant and concurrently develop an early recurrence, with its poor prognosis, or become pregnant during active anticancer treatment which can harm the developing fetus. The most favorable time to attempt conception after breast cancer diagnosis is not currently known due to the lack of large, population-based studies; timing is likely be idiosyncratic to each woman. Factors such as age, disease stage, histological grade, lymph node involvement, hormone receptor status and the type of breast cancer all impact on the type of cancer treatment undertaken, and each treatment has a differing impact on ovarian function. These diverse factors need simultaneous consideration when offering advice to breast cancer survivors on appropriate delays in attempting a subsequent pregnancy. In assessing breast cancer prognosis, the most important variables include lymph node status, tumor size, tumor grade and hormone receptor status. Various algorithms can be constructed which then give a likely prognosis. One of the most widely used of these is found on the adjuvant online website (www.adjuvantonline.com), although it is recognized that this is less precise in very young women due to the small numbers of these women in clinical studies[16,17].

Studies have examined subsequent pregnancies in women previously diagnosed with breast cancer. One recent study of women with localized disease suggests that early conception following the completion of breast cancer management is unlikely to adversely affect survival for women with good prognosis tumors[9]. Moreover, women who conceive after a diagnosis of breast cancer have equivalent or better survival than similar aged women who do not conceive after a diagnosis of breast cancer[9,13,18–24]. This observation suggests that a subsequent pregnancy may provide a positive survival benefit to women. It is important, however, to interpret these studies with caution due to the bias known as the 'healthy mother' effect. Simply stated, only a select group of women with good prognostic tumors become pregnant after a diagnosis of breast cancer (Figure 1). These studies may therefore be prone to selection bias.

POPULATION BASED STUDY OF WOMEN DIAGNOSED WITH BREAST CANCER WHO SUBSEQUENTLY CONCEIVED

A population based study exploring breast cancer and subsequent pregnancy looked at all women under 45 years of age, diagnosed with breast cancer between 1 January 1982 and 31 December 2000 within Western Australia (WA). This huge state has a population of 2.1 million individuals and recorded 25,000 live births and 7000 abortions per annum in

the study period. Of the 2539 women (15–44 years) with a pathologically confirmed diagnosis of breast cancer, 1421 (56%) had naturally conceived at least one full-term pregnancy prior to their diagnosis of breast cancer, and 123 (5%) had at least one pregnancy following their breast cancer diagnosis (median age 31 years at diagnosis and 35 years at first subsequent pregnancy). The women who had a subsequent pregnancy were significantly younger at the time of their breast cancer diagnosis compared to other women aged less than 45 years diagnosed with breast cancer, but when they became pregnant were older than other mothers who had a live birth in WA during the same time period.

Figure 1 A pregnant woman with mastectomy

The types of breast cancers diagnosed within the subsequent pregnancy group, were largely comparable to similar aged women (77% invasive ductal carcinoma, ranging in size from 1 to 90 mm, with half less than 20 mm in diameter). Tumors were reported to be estrogen receptor (ER) positive in 24% of the cases, although 42% had unknown ER status and 64% were lymph node negative.

In this study, as in previous reports, survival was very good, with 85% of women alive at 10-year follow-up, although 37% of women had experienced disease recurrence. Tables 1 and 2 show recurrence-free and overall survival in women who had a subsequent pregnancy after initial breast cancer diagnosis[9]. As seen in the tables, the 5-year overall survival was 91.8% and 10-year overall survival was 78.5%. Recurrence and survival rates were similar whether survival was measured from time of diagnosis or first subsequent pregnancy.

In terms of pregnancy outcomes for the WA study, 175 subsequent pregnancies were confirmed from 123 women previously diagnosed with breast cancer. Over one-third of the

Table 1 Recurrence-free survival from breast cancer diagnosis and from date of pregnancy completion (%)

Recurrence-free time	*From diagnosis*	*From subsequent pregnancy*
5 years	74.5	62.2
10 years	59.8	57.3

Table 2 Overall survival from breast cancer diagnosis and from date of pregnancy completion (%)

Overall survival	*From diagnosis*	*From subsequent pregnancy*
5 years	91.8	87.6
10 years	78.5	84.9

women conceived more than one subsequent pregnancy, with four women experiencing more than three subsequent live births.

The first subsequent pregnancy following a breast cancer diagnosis in these women resulted in a live birth for 66 women (54%). Three women successfully underwent *in vitro* fertilization (IVF) treatment to conceive following their breast cancer diagnosis; they all remained alive and recurrence free at last follow-up. The median time from breast cancer diagnosis to first subsequent pregnancy was 23 months (interquartile range 11–42). There were no stillbirths or ectopic pregnancies. Two births occurred before 36 weeks: a set of twins at 32 weeks following spontaneous rupture of membranes, and a singleton birth by cesarean section at 30 weeks when the mother developed both local and distant metastases. All children were alive and well at last follow-up.

Compared to other women diagnosed with breast cancer when they were less than 45 years of age, women who wait at least 24 months after they have been diagnosed to become pregnant were less likely to die (HR 0.48, 95% CI 0.27–0.83, $p = 0.009$). The likelihood of dying was also reduced for women who waited 6–24 months to become pregnant (HR 0.45, 95% CI 0.16–1.28, $p = 0.135$)[9]; however, this was not a statistically significant finding. Only a few women became pregnant in the 2 years after being diagnosed with breast cancer, but this result suggests that those women who have completed treatment, have good prognosis tumors and are unlikely to have disease recurrence during this time can safely consider pregnancy.

Forty-two (34%) women underwent pregnancy termination. Of the women who terminated their first subsequent pregnancy, ten had at least one subsequent live birth. Three main reasons were given for these terminations: the woman's fear of disease recurrence; the recommendation of the clinician; and the woman having received adjuvant therapy whilst pregnant.

As long as women have completed adjuvant therapy, available evidence suggests that conception within 2 years of a diagnosis of breast cancer does not adversely impact on survival. Consequently, there is no need for some women to wait the full 2 years before attempting conception. However, it is important that this advice be focused on women with good prognosis tumors who are not on adjuvant treatment such as tamoxifen. Available research examining outcomes and survival in those who become pregnant and those who do not shows similar results, but further research will be necessary to corroborate these findings.

FETAL TOXICITY OF BREAST CANCER TREATMENTS

Treatments for early breast cancer in premenopausal women may include local treatments, surgery and radiotherapy, as well as systemic treatments including hormone therapies (tamoxifen, ovarian ablation and ovarian suppression with gonadotropin releasing hormone analogues such as goserelin), chemotherapy and biological agents such as Herceptin. All can be toxic to a developing fetus, particularly in the first trimester of pregnancy. Surgery is fairly safe, although anesthetic consultation concerning risk is required. Radiotherapy is contraindicated during pregnancy[25]. Tamoxifen has potential fetal toxicity, including Goldenhar's syndrome[12,26]. Chemotherapy is likely to be teratogenic in the first trimester of pregnancy, resulting in embryo loss in the very early stages of development and potential fetal damage later on; this is possibly related to the agent used[27]. Data on the use of Herceptin and pregnancy are very limited, but this agent may cause complications, including a decline in the quantity of amniotic fluid[28–37]. This information is important in counseling a woman who may fall pregnant or consider doing so during her breast cancer treatment (Figure 2).

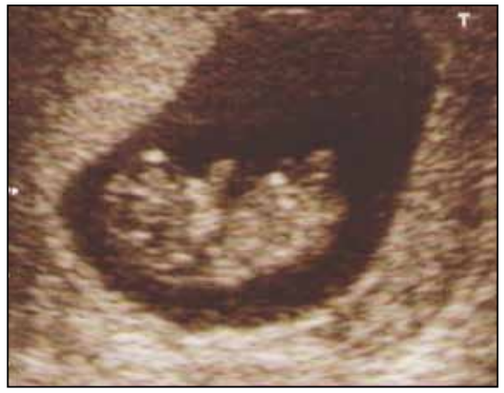

Figure 2 Fetal ultrasound

CONTRACEPTION AND PREGNANCY DURING BREAST CANCER TREATMENT

Anecdotal evidence suggests a number of reasons to explain why women conceive following a diagnosis of breast cancer. The main reason is quite simple, that is, the desire to have a child, especially in women who may have delayed this decision for some years and, unfortunately, are diagnosed with breast cancer in the interim. However, some women have unplanned pregnancies after breast cancer due to lack of contraceptive advice or failure of a contraceptive method.

Whilst breast cancer is being actively treated, it is important that the woman avoids pregnancy, and personalized instruction regarding the use of adequate mechanical forms of contraception, including condoms or the fitting of a diaphragm, becomes a priority. It is essential that contraceptive advice be offered to all pre- and perimenopausal women following their diagnosis of breast cancer for two reasons: first, mechanical contraception is preferred, as the oral contraceptive pill is associated with a potentially increased risk of recurrence[38,39]; and, second, the teratogenic effect that chemotherapeutic or hormonal agents and radiotherapy may have on a developing fetus should a woman conceive during these treatments is real (see above). Moreover, some hormonal agents (including tamoxifen and the aromatase inhibitors) can induce ovulation in premenopausal women[12]. It is thus imperative that younger women be informed of this and realize that tamoxifen is not a contraceptive and can, in fact, stimulate multiple ovulations which may result in multiple pregnancy[4]. Whilst a progestin-only contraceptive agent has been used by women following a diagnosis of breast cancer, the evidence concerning harms and benefits of this type of contraception is unclear, and concern over the potential stimulating effects of progestin is present in both epidemiological[40] and biological[41] literature.

If a woman conceives during active breast cancer treatment, then she should be counseled about the effects that the radio-, chemo- or hormone therapy may have on the fetus. The decision to terminate the pregnancy or not should ultimately be taken by the woman herself, although her partner (if one is present and available) may be consulted; the woman should be supported regardless of her final choice.

FERTILITY AFTER BREAST CANCER DIAGNOSIS

One of the most important issues facing women who have not yet started or completed their families when diagnosed with breast cancer is fertility preservation and/or options for conception after breast cancer treatment is complete. For some women, the opportunity (rather than the reality) to have a child is more important than their own long-term survival. Health professionals need to sensitively assess how individuals feel about preserving their fertility and the importance of maintaining reproductive potential. In the first instance, any woman of reproductive age should be offered referral to a fertility specialist for fertility advice and counseling prior to commencing

treatments such as chemotherapy. Even if they decline the referral, they should be advised of the impact their breast cancer treatment may have on their ability to conceive.

Both cytotoxic and hormone treatments affect fertility[42–44], with 64% of adult females who undergo chemotherapy experiencing some symptoms of ovarian failure[26,27]. Many women become amenorrheic, particularly those aged over 40 years[6]. In women with ER positive tumors, temporary or permanent ovarian failure may be the aim of treatment; however, the survival gains must be weighed against morbidity and patient concerns[45]. Figure 3 compares the number of menopausal women by age based on treatment with or without chemotherapy. As evident in the graph, the number of women who become menopausal after treatment with chemotherapy is significantly higher across all age groups.

Infertility can be devastating for the woman who desperately wants a child. Interventions undertaken before chemotherapy commences can increase the long-term chances of a woman having a biological child. Fertility options currently available, such as IVF, are usually only available to women diagnosed with breast cancer who have a male partner and are planning to have children together. The embryos would then be cyropreserved for use later. To undergo IVF, chemotherapy needs to be delayed for at least 4 weeks while the woman receives fertility drugs. The success rate is not very high, with only about 15% of thawed embryos resulting in a live birth[47]. There is also a concern for women with ER positive breast cancer, that the raised estrogen levels caused by IVF may increase the disease progression. This has yet to be clarified in research studies, although recent data suggest fertility treatment does not increase breast cancer risk in otherwise healthy women[48]. Treatments that include ovarian stimulation, however, may delay the start of adjuvant chemotherapy with as yet unknown consequences on the breast cancer outcome. For some women this delay in the commencement of treatment is unacceptable.

Some research findings indicate that it may be useful to preserve a woman's fertility

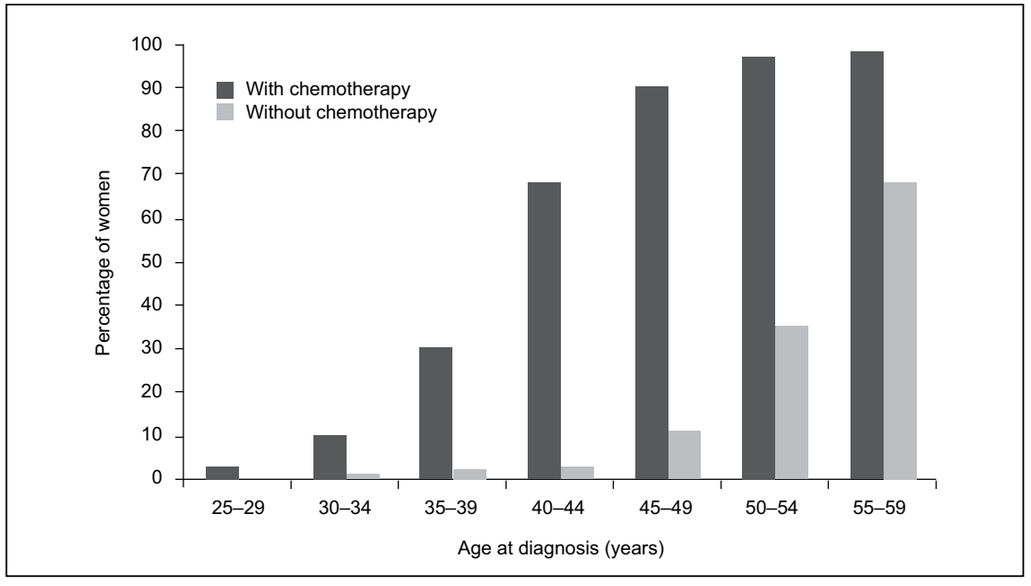

Figure 3 Estimated number of women who become menopausal after chemotherapy depending on their age at diagnosis. Adapted from Goodwin *et al.*, 1999[46]

by suppressing ovarian function for up to 6 months with an agonist whilst the individual is receiving chemotherapy treatment. This would involve reversible chemical sterilization to protect the follicles during therapy using such drugs as goserelin. However, additional research is necessary to explore the safety and viability of goserelin as an ovarian function protector before this can be fully recommended as a fertility option[47]. Currently women are encouraged to enter a clinical trial, if available locally[49].

For premenopausal women who are single at the time of their diagnosis, fertility preserving options are limited, as many options are still in the early stages of development. Available experimental techniques include undergoing therapy with fertility drugs and the retrieval of mature oocytes for freezing and later use. To date this option has resulted in a very low birth rate, so it would need careful consideration in relation to the women's individual cancer and recommended treatment. Surgically removing a wedge of ovarian tissue is another option where, following cryopreservation, the ovarian tissue can be re-implanted. Use of this option has, however, resulted in only a handful of pregnancies worldwide[50–53]. Both techniques are likely to have increased success rates in the future as scientists and clinicians work collaboratively to improve them. Some women may not want to receive any fertility preserving treatment and may wait until after their treatment to find out whether they are able to have children.

Table 3 below shows the known advantages and disadvantages of fertility preserving strategies. As the table shows and was noted earlier, the most effective fertility preserving strategy is IVF and embryo cryopreservation; however, this requires male participation and may not be a viable option for all women. Whilst it may not be possible to preserve fertility for all women, other options for having non-biological children are also available. These include oocyte donation, surrogacy and adoption. For all women who have had a diagnosis of breast cancer, and have endured and completed a course of treatment which has left them infertile, oocyte donation is a reasonable possibility, which should be discussed prior to and after the completion of breast cancer treatment[47]. In reality, it would be useful to discuss all of the available options with individuals whose fertility is unlikely to be preserved and to refer women to relevant sources who can provide further information and counseling about alternative options.

The chances of a woman being able to conceive after a diagnosis of breast cancer are fraught with numerous difficulties. Fertility preservation strategies are still in their infancy and may delay treatment. This is compounded by reduced ovarian function secondary to adjuvant breast cancer treatments and the advice to delay conception for 2 years following breast cancer diagnosis. A decline in already poor ovarian function for women diagnosed with breast cancer in their late 30s and early 40s makes pregnancy more improbable[5]. This has significant clinical implications when advising younger women diagnosed with breast cancer who have good prognostic tumors and want the opportunity to conceive after treatment. It is imperative that full counseling concerning the ramifications of conceiving and raising a child following treatment for breast cancer be part of the management plan for all young women.

The issue of fertility must be discussed with the premenopausal woman at or shortly after a diagnosis of breast cancer. This discussion should be initiated by the health care provider. A woman newly diagnosed with cancer is likely to be overwhelmed with information and will have many pertinent issues to consider. Many women are consumed with issues concerning treatment and survival, and will not be cognisant or aware of the impact of cancer treatment on their fertility.

In order to make an informed choice about her treatment and fertility, it is important

Table 3 Advantages and disadvantages of fertility preserving strategies

Potential fertility preserving strategies	*Advantages*	*Disadvantages*
IVF and embryo cryopreservation	Relatively effective in achieving pregnancy Clinically available	Requires a male partner and embryos legally owned by both partners Likely to increase circulating estrogen levels which may impact on prognosis of ER positive breast cancer May delay chemotherapy In gene mutation, carriers may transmit increased cancer risk to offspring
Ovarian stimulation and oocyte cryopreservation	Does not require a male partner	Very few successful pregnancies Likely to increase circulating estrogen levels which may impact on prognosis of ER positive breast cancer May delay chemotherapy In gene mutation, carriers may transmit increased cancer risk to offspring
Ovarian tissue cryopreservation and xenotransplantation	Does not require a male partner Does not require ovarian stimulation and increased estradiol levels Unlikely to delay chemotherapy	Very few successful pregnancies May reimplant ovarian tissue affected by micrometastases In gene mutation, carriers may transmit increased cancer risk to offspring Surgical procedure
Ovarian suppression with GnRH agonists	Does not require a male partner Simple to administer Unlikely to delay chemotherapy Relatively less invasive	Efficacy in fertility preservation not confirmed Side-effects unknown

ER, estrogen receptor; GnRH, luteinizing hormone releasing hormone; IVF, *in vitro* fertilization. Reproduced with permission from Hickey *et al*., 2009[4]

that the clinician raises the issue of fertility with women prior to the commencement of treatment. If, after the initial discussion with the primary physician, a woman would like the opportunity to consider pregnancy after completing breast cancer treatment, it is absolutely essential that she be referred to a fertility specialist to discuss her options and undergo any necessary procedures before systemic therapy commences[54]. With more young women being diagnosed at an earlier disease stage, and improved and targeted breast cancer treatments available worldwide, women are surviving longer. Given the rapid progress in reproductive medicine of the past decade, it is likely that new and advanced fertility techniques will allow women greater opportunity in the future to conceive after a breast cancer diagnosis.

Health professionals should be able to communicate effectively with all women regarding the options available, detailing the

pros and cons of each treatment and supporting the woman's concerns, whatever they may be. Throughout the consultation process, a woman should be allowed every opportunity to make a decision which is right for her. Anecdotal evidence suggests that impartial and honest communication from the health professional may help to lower a woman's distress and improve her psychosocial well-being, allowing her to make an informed decision regarding her treatment, and improving treatment compliance.

This latter area may need some improvement, as many women report that they were not fully informed or made aware of the adverse consequences of breast cancer treatment on fertility prior to commencing treatment[3,54,55]. A recent study by Thewes *et al*.[3] showed that young women wanted information about fertility and the potential side-effects of treatment at the time of their diagnosis and when making treatment decisions, and that they rated this as highly important.

The decision making process for a woman and/or her partner on whether to undergo fertility interventions prior to treatment is complex. Issues to consider include the type of interventions available, how effective the intervention is, potential delays to the cancer management whilst undergoing fertility treatment, possible long-term health risks, cost of the intervention, and ethical and legal considerations[56]. Unfortunately there are large gaps in our knowledge base, particularly concerning long-term effects, and this can make it difficult for women to make a fully informed decision. A fertility decision aid for young women with early breast cancer has been developed (M. Peate, Sydney, personal communication) which may help individuals to make such a decision prior to commencing treatment; this will shortly be available in the published literature, and on the Australian National Breast and Ovarian Cancer Centre website[57].

MANAGEMENT OF PREGNANCY IN WOMEN WITH A PRIOR DIAGNOSIS OF BREAST CANCER

The obstetric management of a woman who conceives after a breast cancer diagnosis should be the same as for any pregnant woman with a few provisos. Prior to attempting conception the woman should consult her oncologist to ensure that she has no disease recurrence, and any psychological fears should be discussed and addressed. Mothers can breastfeed from the unaffected breast, although this is very unlikely to happen from the affected breast due to the damage caused by radiotherapy. Women who choose to breastfeed may require additional support from midwives or lactation consultants on how to protect their nipple if they are feeding from just one breast.

If disease does recur when the woman has conceived, then the woman should be given all available information on how her cancer can be treated and what measures can be taken to protect her unborn child so that she can make an informed decision about her treatment and her pregnancy. A multidisciplinary approach including the cancer surgeons and physicians, and obstetric health professionals should be used and the pregnancy treated as high risk.

CONCLUSIONS

Women with breast cancer welcome the option to discuss and explore the fertility and pregnancy options available to them prior to commencement of their treatment. In fact, this is essential to promote women's well-being and can increase treatment compliance later on. Effective communication is at the forefront of this approach, and we encourage health professionals working with women diagnosed with breast cancer to approach fertility at the outset of treatment. This is of paramount importance to women and building a positive rapport

surrounding this issue can help and facilitate each individual woman's cancer journey.

It is important to consider future fertility options at the time of breast cancer diagnosis and treatment, as part of the multidisciplinary care of young women with breast cancer.

Women who conceive after a diagnosis of breast cancer find that children bring normalcy back into their lives and allow them to think about something or someone other than their own health[58].

Women diagnosed with breast cancer who conceive have a similar survival compared with those who do not, when taking into account the likelihood that only those with better outlook tumors will go on to have children. When time to pregnancy was accounted for, an increase in survival was only significant for women who waited at least 24 months to conceive. These results provide evidence for the clinical recommendation that women delay pregnancy for 2 years after a diagnosis of breast cancer but may suggest that women who have a good prognosis need not wait 2 years to become pregnant. While some women will choose not to become pregnant after their breast cancer diagnosis, an increasing number of women are likely to want the option of having children. For women with localized disease, conception following the completion of their breast cancer management is unlikely to adversely affect their survival.

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27

Preconceptional optimization in the solid organ recipient

Sarah Jones and Sue Carr

INTRODUCTION

Impaired fertility is common in women with end-stage organ disease. Amenorrhea occurs in approximately 50% of patients with chronic liver disease[1], and in many women with advanced chronic kidney disease (CKD)[2]. Abnormalities of the hypothalamic–pituitary axis and hormonal abnormalities are commonly implicated. In women with end-stage renal disease (ESRD), subfertility may also occur due to hypothalamic–gonadal dysfunction[3]. For women with liver disease, menstrual dysfunction may be linked to the etiology of the underlying liver disease[1]. Pregnancy is an uncommon event in women with advanced CKD; each year pregnancy only occurs in 0.5% of women of childbearing age treated with dialysis[4]. Despite this, unplanned pregnancies do occur, and all women of childbearing age with end-stage organ disease should be provided contraceptive advice.

Following organ transplantation, fertility in women of childbearing age is usually swiftly restored, typically within 6 months[5]; for many young women with end-stage organ disease, transplantation offers the best chance of a successful pregnancy. The first successful pregnancy following renal transplantation was reported in 1958[6] and after orthotopic liver transplantation in 1978[7]. Since then, successful pregnancies have been reported in recipients of lung, heart and pancreas-liver transplants. Today approximately 2% of women of childbearing age with a renal transplant become pregnant[9], and the literature now contains reports of over 14,000 pregnancies worldwide[8]. The US National Transplantation Registry reported that more than 70% of post-transplant pregnancies result in a successful live birth[9].

Despite good pregnancy success rates, women with solid organ allografts are at increased risk of complications during pregnancy including hypertension, pre-eclampsia, preterm delivery and infection[1,10]. Because some immunosuppressive agents and other medications commonly used in transplant recipients are contraindicated in pregnancy, these issues merit discussion with women of childbearing age. Ideally such discussions should occur prior to transplantation in order for pregnancy to be planned at the optimum time in terms of maintaining good graft function and minimizing the likelihood of complications to mother and baby.

OPTIMAL TIMING OF PREGNANCY AFTER TRANSPLANTATION

Restoration of fertility, and hence the ability to conceive, usually occurs fairly rapidly following successful organ transplantation[8]. The recovery of fertility is less common in women who undergo transplantation towards the end

of their childbearing years[11], and irregular menstrual bleeding remains a major concern of women with a renal transplant. In one study of 114 patients, although 49% had normal menstruation, another 31.2% had oligomenorrhea, hypomenorrhea or amenorrhea[12]. In the early post-transplant period, pregnancy is less likely to be successful when the degree of immunosuppression and the risk of acute rejection and infection all are generally highest. It is therefore important that appropriate contraceptive advice be given to women prior to organ transplantation. Although the choice of contraceptive method is essentially arbitrary, many physicians prefer long-acting forms of contraception to ensure adequate protection[8]. Intrauterine devices are less likely to be effective in patients taking immunosuppressive agents because their efficacy depends on intact immunologic function[13]. They may also increase the risk of intrauterine infections[10].

Historically, most transplant centers have advised that pregnancy is safe after the second post-transplant year, providing that the graft is functioning well. For renal transplant recipients, this typically means a serum creatinine of less than 133 μmol/l (<1.5 mg/dl) and urine protein excretion of less than 500 mg/day[14]. In 2003, a consensus conference held by the Women's Health Committee of the American Society of Transplantation (AST) concluded that pregnancy is probably safe after the first transplantation year, providing that allograft function is stable and no episodes of rejection have occurred in the year preceding conception[15]. At this point the patient is usually stable, the risk of an acute rejection episode is generally low, immunosuppressive medication will have been reduced, and viral prophylaxis will have been completed[8].

Specific guidelines for recipients of other solid organ transplants regarding allograft function prior to conception are lacking[9]. Cardiac transplant recipients are advised to avoid pregnancy for at least 1 year post-transplantation and preferably 2 years[16]. For recipients of lung transplants, most expert opinion in published series recommends waiting at least 2 years before conception[17]. Acute rejection is common in the first year, with over 50% of patients requiring treatment. Two years after lung transplantation, however, the risk of acute rejection is reduced, and as with other solid organ transplants recipients, patients will be maintained on lower doses of immunosuppression[18].

The optimal timing for a pregnancy for a woman with a solid organ transplant is probably somewhere between 12 months and 5 years post-transplant[19]. In addition to stable graft function and absence of recent rejection episodes, immunosuppression should be at stable dosing, and acute infections which might affect the fetus should not be present (see Figure 1). A number of special circumstances can affect adherence to the published recommendations[15], including maternal age, medical noncompliance and additional comorbidity factors that may impact on graft function and pregnancy. On the occasions when women who do not fulfil the recommended criteria regarding timing of pregnancy choose to become pregnant or accidentally conceive, such cases must be assessed on an individual basis.

Any pregnancy in a solid organ transplant recipient should be considered high risk. The expectant mother should be managed by a multidisciplinary team including her transplant physician and an obstetric specialist with expertise in this field, and should be monitored on a frequent basis[20]. Particularly close surveillance is recommended for diabetic women with renal allografts, because complications are more frequent in this group[10]. Following a successful pregnancy, both allograft function and levels of immunosuppressive drugs require close monitoring; regular postpartum follow-up should be ensured.

Some transplant recipients desire more than one pregnancy. In this eventuality, it is important that the entire clinical picture be reassessed prior to each pregnancy, i.e. graft

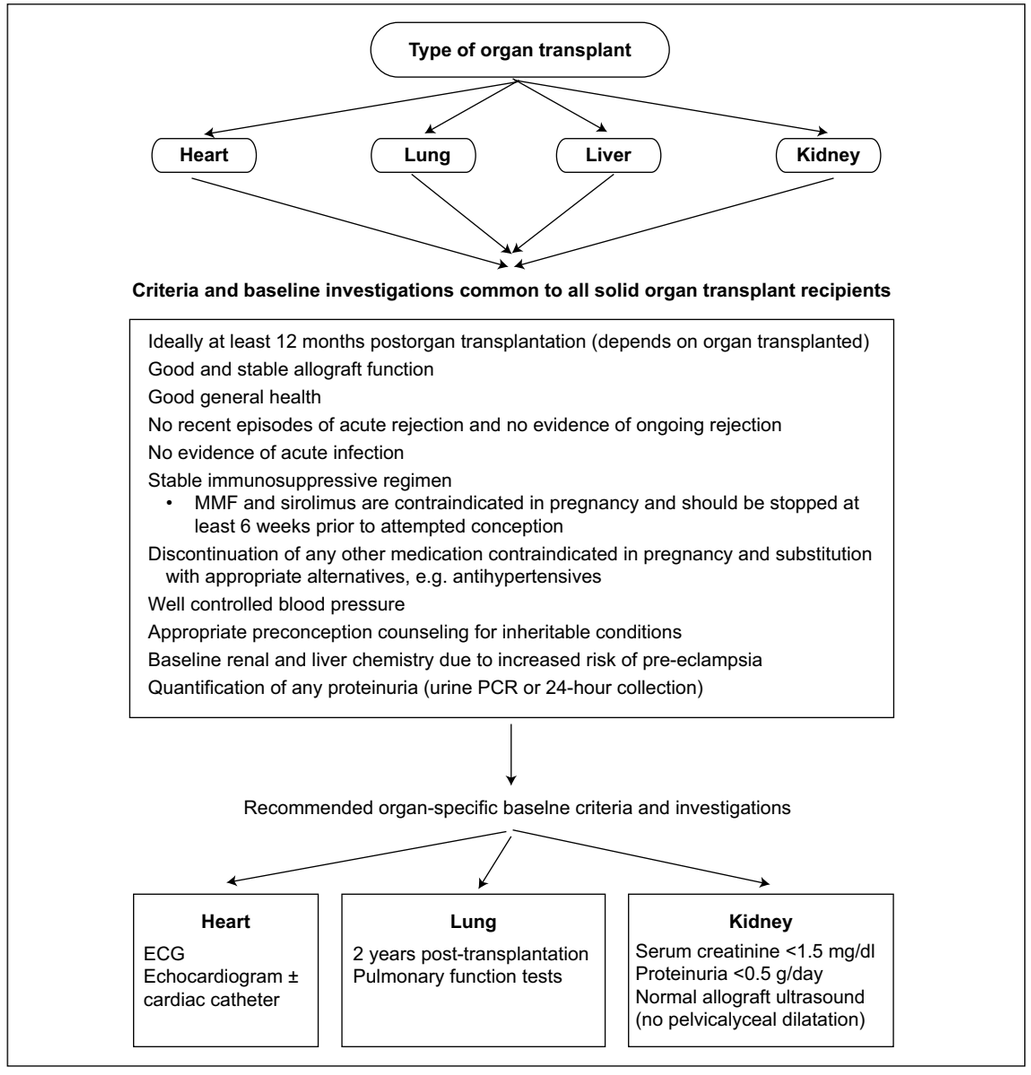

Figure 1 Criteria for considering pregnancy in solid organ transplant recipients. MMF, mycophenolate mofetil; PCR, protein to creatine ratio; ECG, electrocardiogram

function, hypertension, renal dysfunction and proteinuria, and that the risks posed by any new medical problems be assessed. Evidence from the European Dialysis and Transplant Association (EDTA) registry shows that further pregnancies do not adversely affect graft function provided that graft function is good at the onset of each pregnancy[21].

PRECONCEPTION COUNSELING

Preconception counseling, preferably offered by a multidisciplinary team including obstetricians, transplant physicians, midwives, pharmacists and other health professionals, should be offered to the solid organ transplant recipient and her partner, ideally prior

to transplantation[1,10,17]. All patients should be offered contraceptive advice. Any patients hoping for a future pregnancy should be counseled about the potential risks of pregnancy to the mother and child, timing of pregnancy and, if appropriate, alternative options.

Solid organ transplant recipients who have difficulty conceiving naturally are likely to seek access to assisted reproductive techniques such as ovulation induction, *in vitro* fertilization and embryo transfer[19]. In one study of 126 Iranian renal transplant recipients, the rate of infertility (10.4%) was similar to that of the general population[22]. There are case reports of successful *in vitro* fertilization in female renal transplant recipients[23,24] and also of intracytoplasmic sperm injection for male renal transplant recipients with infertility[25].

BASELINE PRECONCEPTION ASSESSMENT IN THE ORGAN TRANSPLANT RECIPIENT

For recipients of cardiac transplants, a number of baseline tests are required to assess cardiac status prior to pregnancy. All patients should have an electrocardiogram and an echocardiogram[17]. Some experts advocate coronary angiography (to exclude allograft coronary artery disease), right heart catheterization and cardiac biopsies, but these tests may not be required if the patient is stable from a cardiovascular point of view. Likewise, pulmonary function should be assessed with appropriate tests in the lung transplant recipient, and most experts recommend that spirometry should be performed regularly during the pregnancy[26,27]. Patients with a renal transplant should have an ultrasound of the allograft to ensure there is no pelvicalyceal dilatation[14].

It is not uncommon for recipients of both lung and heart transplants to have a degree of renal dysfunction which requires assessment prior to conception. Renal chemistry should be checked, and proteinuria quantified by either a urine protein to creatinine ratio (PCR), or a 24 hour urine collection[17]. Given the increased risk of pre-eclampsia in this group of patients, baseline liver chemistry should also be checked so comparison can be made to assist with diagnosis if pre-eclampsia is suspected[17]. Figure 1 summarizes the baseline and organ-specific investigations which should be undertaken when pregnancy in solid organ transplant recipient is being considered.

SPECIAL CIRCUMSTANCES

The underlying reason for organ transplantation may have implications for the pregnancy and well-being of the fetus[17]. A number of renal diseases have a hereditary component, and women need to be informed on how their kidney disease may affect their child. Vesicoureteric reflux (VUR) is one such condition and, in many cases, is probably inherited in an autosomal dominant manner. It is commonly diagnosed in pregnancy when often previously asymptomatic women develop recurrent urinary tract infections, hypertension and proteinuria[28]. Women with VUR must be advised that their child may inherit the same condition. If the maternal diagnosis is known during the pregnancy, antenatal ultrasound may be used to look for the typical changes of reflux nephropathy in the fetus[29]. Patients with adult polycystic kidney disease (APKD) or a family history of Alport's syndrome can be referred for genetic counseling[28].

For women whose underlying liver disease was caused by a genetic disorder such as alpha-1 antitrypsin deficiency and hemochromatosis, or even rarer conditions such as Alagille syndrome and Caroli syndrome, genetic counseling should be offered. Prenatal testing may be available for certain conditions[1].

Lung transplant recipients who had cystic fibrosis (CF) prior to transplantation should be offered genetic counseling as recommended by the American College of Obstetricians and Gynecologists (ACOG)[30]. Their partners should be offered carrier testing to determine the risk of CF in any future offspring.

For patients who underwent cardiac transplantation due to peripartum cardiomyopathy (PPCM), there is a theoretical risk of recurrent PPCM. Some published case reports have not demonstrated any evidence of disease recurrence; however, the number of cases reported is currently too small to draw any conclusions[17].

For women with congenital heart disease the risk of recurrence in the offspring is up to 8%, depending on the nature of the maternal lesion[31]. Cardiac transplantation in patients with mitochondrial myopathies has been reported[32]. There is a risk that these and other conditions can be transmitted to offspring, and for this reason appropriate preconception genetic counseling should be offered to any woman who is at risk.

VACCINATION

Most patients should be offered appropriate vaccination as part of routine pretransplant medical care. If not already immunized, prior to conception the patient should be vaccinated against influenza, pneumococcus, hepatitis B and tetanus[17]. Women who are not rubella immune should receive the rubella vaccine before being transplanted, because live virus vaccines are contraindicated post-transplantation[11].

OPTIMIZATION OF IMMUNOSUPPRESSION

Immunosuppressive agents must be continued during the pregnancy to avoid graft rejection, but the benefits to the mother should be balanced with potential detrimental effects to the fetus. All medications used to prevent rejection of transplanted organs cross the maternal–placental–fetal interface[8], but fortunately the location of the fetal liver facilitates filtration of all pharmacological agents that cross the placenta.

To date the immunosuppressive regimens in most of the successful pregnancies in allograft recipients have consisted of a combination of prednisonlone, azathioprine and a calcineurin inhibitor (CNI) – either cyclosporine or tacrolimus[5]. Prednisolone should ideally be at a dose of less than 15 mg/day, and azathioprine less than 2 mg/day[14]. CNI dose adjustments are often required during pregnancy. Whilst the consensus from the literature is that acute rejection rates during pregnancy are low and are indeed no higher than in non-pregnant patients, CNI levels can fluctuate during pregnancy, a factor which can increase the likelihood of an acute rejection episode. Cyclosporine levels can fall during pregnancy, thus necessitating a 33% increase in dose after 20 weeks[33]. However, the authors of this same report found that postpartum drug levels can rise sharply, and further dose adjustments were necessary to avoid toxicity. It is mandatory that CNI levels are monitored closely both during pregnancy and in the immediate postpartum period. Although neither cyclosporine nor tacrolimus has been reported to be teratogenic or mutagenic, both have been associated with low birth weight, intrauterine growth retardation and small size for gestational age infants[5]. In this regard, patients with hyperemesis gravidarum may have inadequate immunosuppression levels due to reduced absorption.

Data regarding the safety of newer agents such as mycophenolate mofetil (MMF) (Cellcept) and sirolimus are more limited but progressively increasing. MMF, a prodrug of mycophenolic acid, is now used worldwide as an immunosuppressive agent following solid organ transplantation[34]. In combination with prednisolone and often tacrolimus it is typically used as first-line immunosuppression in the USA and mainland Europe following renal transplantation[35]. Systemic

lupus erythematosus (SLE) which commonly affects young women of childbearing age can be treated with MMF, particularly if there is severe renal involvement[36]. According to the annual report of the Organ Procurement and Transplantation Network in the United States, MMF use for immunosuppression after renal transplantation increased from 11.9% in 1995 to 79.6% in 2000[37]. This agent is known to have teratogenic properties in animals, with offspring of treated rats and rabbits showing increased frequencies of anophalmia, agnathia, hydrocephaly, cardiovascular and renal abnormalities, as well as umbilical and diaphragmatic hernias[38,39].

A number of case reports presently describe congenital abnormalities following human maternal mycophenolate use. In one report of a pregnancy terminated at 22 weeks during which the mother was treated with MMF at the time of conception and during organogenesis, the fetus exhibited multiple malformations[40] including cleft lip and palate, micrognathia, ocular hypertelorism, microtia and external auditory duct atresia and a left pelvic ectopic kidney. In addition, complete agenesis of the corpus callosum was present. In 2007, Perez-Aytes *et al*.[34] reported a newborn with a number of congenital abnormalities including cleft lip and palate, bilateral microtia, hypertelorism and micrognathia whose mother, a renal transplant recipient, had become pregnant whilst taking MMF. At that time an extensive literature review identified six other cases with similar malformations after *in utero* exposure to MMF.

The MMF manufacturer's Summary of Product Characteristics states that its use is not recommended during pregnancy and should be discontinued at least 6 weeks before conception is attempted, during which time effective contraception should be used. Therapy with MMF should not be initiated until a negative pregnancy test has been obtained. Female patients should be informed that congenital malformations, notably involving development of the ears, have been reported in children of patients exposed to MMF in combination with their other immunosuppressants during pregnancy. The manufacturers also advise that MMF is contraindicated in nursing mothers.

Sirolimus (rapamycin) is a potent macrolide immunosuppressive agent used frequently following organ transplantation. Currently data are limited on the impact of sirolimus on pregnancy outcomes. Studies in pregnant rats have shown that whilst sirolimus is not teratogenic, it caused reduced fetal weight and delays in ossification (Summary of Product Characteristics). A case was described wherein a 30-year-old renal transplant recipient delivered a healthy normal baby at term having taken sirolimus throughout the pregnancy[41]. However, based on the current available information, the most recent European Best Practice Guidelines recommend that sirolimus, like MMF, be discontinued 6 weeks before conception is attempted and avoided in breastfeeding mothers[14].

IMMUNOSUPPRESSION AND MALE FERTILITY

Fertility in male patients with end-stage organ disease is reduced for a number of reasons, including low testosterone levels, and high follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin levels which result in abnormalities in spermatogenesis and impotence[42,43]. As is the case in female patients, fertility improves following transplantation due to restoration of hypothalamic–pituitary function resulting in improved sperm motility, although sperm count and morphology are not completely restored to normal[44]. The true incidence and prevalence of male infertility is difficult to determine[43].

The effects of the different immunosuppressive agents on fertility in male transplant organ recipients are not entirely known[43]. Neither azathioprine nor calcineurin inhibitors

(cyclosporine, tacrolimus) are associated with male infertility after transplantation[45]. The effects of MMF on male fertility are largely unknown. The CellCept Summary of Product Characteristics states that MMF had no effect on the fertility of male rats at doses above those used in renal and cardiac transplant recipients. Isolated reported cases of male infertility exist in patients treated with MMF worldwide.

Reports indicate that sirolimus is associated with altered sex hormone levels (low testosterone and elevated LH and FSH) and impaired sperm quality. Deutsch *et al.* reported a case of sirolimus-associated infertility in a young male heart-lung recipient[46]. Sperm quality improved following the withdrawal of sirolimus and the patient subsequently reported fathering a successful pregnancy. The authors postulated that oligospermia is a possible and partly reversible side-effect of sirolimus and this eventuality should be taken into consideration when sirolimus is administered to young male patients. It is probably advisable to avoid sirolimus in male patients who wish to become fathers.

BREASTFEEDING

For most of the commonly used immunosuppressive agents, limited data are available on what to advise women about breastfeeding. Prednisolone appears to be safe to use in the breastfeeding mother[35]. The British National Formulary (BNF) states that systemic effects in an infant are unlikely with a maternal dose of prednisolone up to 40 mg daily[47]. With higher doses, however, it is advised that the infant's adrenal function should be monitored. Milk concentrations range from 5 to 25% of maternal blood levels, and only trace amounts are found in breast milk following a 10 mg dose[48].

Azathioprine has a toxic metabolite which is present in milk in low concentrations. However, small studies have shown no evidence of harm in the babies of azathioprine-treated lactating women[49], and consensus opinion is that breastfeeding is not absolutely contraindicated[15].

The BNF advises that breastfeeding should be avoided in women prescribed tacrolimus and cyclosporine, as both drugs appear in the breast milk[47]. Despite this, several experienced renal transplant units in the UK have permitted breastfeeding in women treated with cyclosporine and no drug-related problems have been noted in their babies[35]. Two reports have identified minimal transfer of tacrolimus to infants as a consequence of breastfeeding[50,51]. As with azathioprine, the consensus opinion for tacrolimus is that breastfeeding is not absolutely contraindicated, but babies should be closely monitored and immunosuppressive levels in the infant should be checked[15].

Given the lack of data on breast milk transfer in lactating women treated with MMF and sirolimus, it is advised that breastfeeding be avoided in women taking these drugs[35].

RISK OF REJECTION

It has been suggested that organ rejection during pregnancy should not occur, because non-specific systemic maternal immunosuppression exists to prevent the mother rejecting the fetus[52]. However, reports have indicated that rejection rates in solid-organ transplant recipients are no different to those in non-pregnant recipients[14,53]. If immunosuppression is reduced during pregnancy based on an assumption of natural non-specific maternal immunosuppression, organ rejection may ensue[8]. Two maternal deaths occurred when immunosuppression was discontinued during pregnancy[8,54]. In cardiac transplant recipients, there is a high risk of acute rejection in pregnancy if immunosuppression is not carefully monitored. It is difficult to confirm the diagnosis of acute rejection in this group of patients as a biopsy usually involves X-ray screening which is contraindicated in pregnancy.

It may be difficult to detect allograft dysfunction during a pregnancy. For recipients of a renal allograft, for example, there may only be a small increase in serum creatinine[55]. The increased glomerular filtration rate which occurs in pregnancy usually results in a fall in serum creatinine[19]. The magnitude of this decline in the renal transplant recipient is dependent upon pre-pregnancy renal function[56].

For patients with liver transplants, any deterioration in liver chemistry during the pregnancy requires aggressive evaluation. There is no contraindication to liver biopsy, if required, to look for evidence of rejection[1]. Derangement of liver chemistry can also occur during pregnancy with pre-eclampsia, HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome and cholestasis of pregnancy. It can be difficult to distinguish these complications from graft rejection and exacerbation of underlying liver disease such as hepatitis C[1].

Methylprednisolone is most commonly given to treat an acute rejection episode and is usually effective[57]. Newer agents such as basilixmab and antithymocyte globulin (ATG) may also be effective but data about their safety in pregnancy are limited[8]. The AST guidelines advise the use of intravenous immunoglobulin, but that ATG and rituximab should be avoided in pregnancy[15].

OPTIMIZATION OF COMORBID CONDITIONS

Many recipients of solid organ transplants often have one or more coexisting medical conditions which may influence the outcome of their pregnancy[58]. It is important that these conditions be identified, and that a management plan be formulated by the relevant multidisciplinary team for antenatal and postnatal care.

Hypertension

Hypertension is a common medical disorder of pregnancy, which affects approximately 10–15% of all pregnancies[59]. It is a major cause of maternal morbidity and mortality, both within the UK and worldwide[60]. As one of the most important factors contributing to pre-eclampsia and resulting increases in the risk of fetal growth restriction, placental abruption and preterm delivery, maternal hypertension is an important factor increasing perinatal morbidity and mortality.

Hypertension is common in the solid organ transplant recipient even before pregnancy, and particularly if the patient is receiving a calcineurin inhibitor such as cyclosporine[61]. The incidence rates of both hypertension and pre-eclampsia vary depending on the organ transplanted[8].

Forty-three to 73% of renal transplant recipients are hypertensive before pregnancy[62] and a further 25% become hypertensive during pregnancy[63,64]. Pre-eclampsia develops in 15–37% of renal transplant recipients[58] and is reportedly as common in recipients of pancreas-kidney transplants[8]. Lower rates have been reported in liver, heart and lung recipients[53]. Hypertension develops in 51% of patients within 1 year of lung transplantation, and by 5 years is present in 85% of these patients[17]. The National Transplantation Pregnancy Registry (NTPR) reported that hypertension during pregnancy occurs in 35% of liver transplant recipients[62]. In 2004 the NTPR reported a 46% rate of hypertension and a 10% rate of pre-eclampsia in pregnant heart transplant recipients[62]. This registry also reported 15 pregnancies and eight live births in lung transplant recipients, finding a 53% rate of hypertension and a 13% rate of pre-eclampsia among these individuals.

Table 1 shows the percentage of women who develop hypertension and pre-eclampsia during pregnancy according to the organ transplanted.

Good blood pressure control has a beneficial effect on both graft and patient survival for recipients of renal transplants[65,66]. There is no specific evidence regarding target blood pressure level in pregnancy, but recent UK consensus guidance recommends that it should ideally be maintained at less than 140/90 mmHg in order to minimize progression of any

Table 1 Characteristics of pregnancy among transplant recipients during pregnancy and of their infants, according to organ received

Characteristic	*Kidney*	*Liver*	*Pancreas and kidney*	*Heart*	*Lung*
No. of recipients	751	106	37	39	13
No. of pregnancies	1139	182	53	63	14
Hypertension during pregnancy (%)	28–72	22–42	75	47	50
Diabetes during pregnancy (%)	3–12	0–13	2	4	21
Rejection episodes (%)	2–12	0–11	6	22	31
Pre-eclampsia (%)	29–31	13–33	33	10	13
Graft loss within 2 years (%)	4–14	3–9	17	0	23
Live birth (%)	71–78	72–82	80	70–80	57
Mean duration of gestation (weeks)	35–36	37–38	34	37–38	35
Mean birth weight of infant (g)	2308–2493	2635–2802	2128	2717–2930	2285
Cesarean section (%)	46–92	22–42	52	29–100	38

Reproduced with permission from McKay and Josephson[8]

underlying renal impairment, reduce maternal cardiovascular risk and preserve graft function[58]. No formal guidelines exist for recipients of other solid organs, but it is universally accepted that blood pressure should be well controlled prior to conception[1].

Many solid organ transplant recipients who are planning pregnancy are prescribed one or more antihypertensive agents. It is essential that these are reviewed ideally before conception is attempted, or at the time pregnancy is confirmed, as some agents are contraindicated in pregnancy.

Methyldopa is usually recommended as the first-line treatment for hypertension in pregnancy[14]. Its safe use in pregnancy has been established in case–control studies, and long-term studies of children whose mothers took methyldopa during pregnancy have shown no adverse effects[67,68]. Women should be informed of its potential side-effects including drowsiness and depression[58].

Several other antihypertensive agents are considered safe in pregnancy. Atenolol is associated with small-for-gestational age babies and should be avoided in pregnancy[69]. Other beta blockers are safe in pregnancy and labetalol is typically used. This class of drug should be avoided in patients who are asthmatic. Calcium channel blockers appear to be safe and well tolerated[70], and follow-up at 18 months has shown no detrimental effects in the infants[71]. Although there have been few controlled trials to demonstrate its safety, hydralazine has been extensively used in pregnancy with few adverse events reported. It is commonly used as adjunctive therapy with methyldopa[72].

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (ARBs) are commonly used in renal transplant recipients to both control blood pressure and reduce proteinuria. Recent reports have linked their use to the development of congenital abnormalities during all three trimesters of pregnancy and these agents are therefore contraindicated in pregnancy[8]. Ideally they should be discontinued before conception is attempted or at the time a pregnancy is suspected or confirmed. A recent study reported a 2.7 times greater risk of serious congenital malformation following exposure to ACE

inhibitors during the first trimester of pregnancy[73]. During the second and third trimesters they are associated with a fetopathy comprising oligohydramnios, hypocalvaria, fetal growth restriction, renal dysplasia, anuria, renal failure and often intrauterine death[74].

Some renal transplant recipients take a diuretic to help control edema which may have arisen secondary to proteinuria, due to either recurrent disease or chronic allograft nephropathy[19]. Diuretics ideally should be avoided in pregnancy because they can cause hypovolemia and thus compromise placental blood flow. However, in cases of severe edema the risk–benefit ratio of diuretic therapy should be assessed on an individual basis.

REDUCING THE RISK OF PRE-ECLAMPSIA

Low-dose prophylactic aspirin helps prevent pre-eclampsia[75]. Few studies, however, have specifically examined the purported benefit in women with underlying renal disease or recipients of organ transplants. Solid organ transplant recipients are at increased risk of pre-eclampsia, and additionally may have other conditions such as diabetes, chronic hypertension and systemic lupus erythematosus that increase the risk further. It is generally recommended that aspirin be commenced after 12 weeks in the high-risk patient if there are no contraindications[58].

Diabetes

A patient with a renal transplant may have had end-stage renal disease due to diabetic nephropathy. Alternatively, a solid organ transplant recipient may have developed new-onset diabetes after transplantation (NODAT)[58]. Patients prescribed steroids and tacrolimus are at increased risk of glucose intolerance. One meta-analysis shows that the risk of post-transplant diabetes is five times greater in patients treated with tacrolimus rather than cyclosporine[76]. For this reason, glucose tolerance testing may be indicated during pregnancy for tacrolimus-treated patients. A recent review reported that 3–12% of pregnant renal transplant recipients had diabetes[8,62].

Pregnant solid organ transplant recipients with diabetes have a number of important issues to consider. For example, the risk of preterm delivery and pre-eclampsia is increased[58] and fetal growth restriction is less common. Significant proteinuria can be present in patients with diabetic nephropathy affecting a transplanted kidney, especially if ACE inhibitors and ARBs have been discontinued at conception. Thromboembolic risk is increased in these patients and prophylactic low-molecular-weight heparin (LMWH) may be necessary. Edema and severe nephrotic syndrome may require diuretic treatment[58].

A patient whose diabetes is normally treated with oral hypoglycemic agents may require insulin during pregnancy. Metformin, currently undergoing a clinical trial, has been used in pregnancy in Australia[77].

Systemic lupus erythematosus and other autoimmune conditions (see also Chapter 7)

Approximately 1–2% of patients on the renal transplant waiting list have end-stage renal disease secondary to lupus nephritis; pregnancy is often a consideration for this category of renal transplant recipients, because SLE commonly affects young women[58]. A number of potential problems need to be considered in the solid organ transplant recipient with an underlying diagnosis of SLE. Recurrent miscarriages can occur. The presence of lupus anticoagulant and anticardiolipin antibody may necessitate treatment with prophylactic LMWH during pregnancy. The presence of anti-Ro and anti-La antibodies increases the

risk of fetal cardiac problems, including complete heart block. As with diabetes, SLE is associated with increased risk of both preterm delivery and pre-eclampsia.

INFECTION

As a consequence of immunosuppression, all recipients of solid organ transplants are at increased risk of infections from bacterial, fungal and viral organisms. Any such infection may pose serious risk to both mother and fetus. The overall risk of infection during pregnancy varies according to the organ transplanted. In lung transplant recipients, it is about 20%[62] and respiratory infections occur most frequently. For recipients of cardiac transplants the infection risk is about 11%[62].

Bacterial infections

Asymptomatic bacteriuria is fairly common during pregnancy, affecting 2–10% of women. Untreated, approximately 30% will develop a symptomatic urinary tract infection (UTI)[58]. Acute pyelonephritis occurs relatively frequently in patients whose end-stage renal disease has been caused by chronic pyelonephritis or reflux nephropathy. The European Best Practice Guidelines (EBPG) recommend that all renal transplant recipients should be screened for bacteriuria on a monthly basis with a midstream urine sample. If asymptomatic bacteriuria is present, a course of antibiotics should be given[14]. Renal transplant recipients frequently suffer from recurrent UTIs, and it is necessary to commence or continue prophylactic antibiotics during pregnancy with a safe agent. Women prescribed trimethoprim should be advised prenatally about changing to alternative antibiotic prophylaxis as this drug should be avoided in early pregnancy[47]. Prophylactic antibiotics are recommended for organ recipients requiring invasive procedures during the pregnancy, including fetal monitoring with scalp electrodes or intrauterine pressure monitoring[72].

Viral infections

Following solid organ transplantation, recipients are potentially at risk of either primary cytomegalovirus (CMV) infection or of reactivation. CMV is the most common cause of viral infection post-transplantation, the risk of which is highest during the first post-transplantation year when levels of immunosuppression are commonly at their peak. The British Transplantation Society recommends that prophylaxis against primary CMV infection with ganciclovir, valganciclovir or valaciclovir should be offered to CMV seronegative patients who receive a solid organ transplant from a donor who is seropositive[78]. Prophylaxis is also advised in cases where the donor and recipient are both seropositive and the recipient is treated with ATG/ALG/OKT3. Ganciclovir is contraindicated in pregnancy as it is teratogenic. It is recommended that effective contraception (including barrier contraception for men) be used during the course of treatment and for at least 90 days afterwards[47]. The same applies to valganciclovir, as it is an ester pro-drug of ganciclovir. Valaciclovir is a pro-drug of aciclovir. Aciclovir is not known to be harmful in pregnancy, but its manufacturers advise that is only used during pregnancy when the potential benefits outweigh any risks[47].

The overall frequency of CMV infection in pregnant transplant recipients is unknown; the NTPR reported four such cases[20]. In pregnancy, CMV infection can result in prematurity and low birth weight. Approximately 90% of congenital infections are asymptomatic. Affected children typically present in childhood with impaired psychomotor development and neurological, hearing, visual or dental abnormalities. Infants with symptomatic CMV infection

can develop jaundice, splenomegaly and a petechial rash. Cytomegalovirus inclusion disease, a severe form of CMV infection, is characterized by multiorgan involvement including microcephaly, seizures and motor disability[58]. By delaying pregnancy for at least 12 months and thus avoiding the period when the need for heavy immunosuppression is greatest, female solid organ transplant recipients can reduce the risk of CMV infection and its potentially serious consequences.

If CMV infection is suspected, a blood sample should be sent urgently for detection and quantification of CMV DNA using quantitative polymerase chain reaction (PCR)[78]. Women who are not immune to cytomegalovirus should be counseled regarding preventative measures.

Herpes simplex virus (HSV) infection is one of a number of persistent viral infections that can occur in solid organ transplant recipients[58]. HSV infection prior to 20 weeks' gestation is associated with an increased risk of abortion[72]. Vertical transmission can occur at the time of vaginal delivery, and cesarean delivery reduces the risk of transmission. Aciclovir can be used in pregnancy[20].

Women not immune to varicella zoster should be advised to avoid contact with individuals with chicken pox. Should exposure occur, prophylactic intervention with intravenous immunoglobulin should be considered.

Hepatitis B and hepatitis C

The hepatitis B and C status of the female organ transplant recipient should be established prior to conception. The prevalence of both hepatitis B virus (HBV) and hepatitis C virus (HCV) infections is increasing in patients with end-stage renal disease on dialysis[58]. If a patient is found to be positive for hepatitis B or hepatitis C the management of a pregnancy should involve close liaison between hepatologists, obstetricians and transplant physicians.

Hepatitis B Patients positive for HBV but without evidence of liver disease are increasingly considered for renal and other organ transplantation[58]. Some patients acquire HBV following transplantation. For those patients who are HBV DNA positive, antiviral therapy is required which may need to be long term. Lamivudine should be avoided during the first trimester of pregnancy[47]. Renal transplant recipients with HBV infection have reduced survival and are at increased risk of graft loss, although outcomes are improving with new developments in antiviral therapy[79].

In general for women who are hepatitis B carriers, pregnancy is uneventful[58]. Exacerbation of disease during pregnancy is uncommon. There is, however, a significant risk of vertical transmission to the infant during delivery, which occurs in up to 80% of cases. The combination of hepatitis B vaccination and hepatitis B immunoglobulin is 95% effective in preventing infection in the neonate[19].

Hepatitis C Hepatitis C is now more common than hepatitis B in renal transplant recipients[19], in that 11–49% of the recipients are reported to be HCV positive[80,81]. The risk of post-transplant liver disease is increased in these patients, and viral replication, and hence viral load, can be increased as a consequence of immunosuppression. The effect of HCV infection on both patient and graft survival following organ transplantation is currently unclear. Ribavarin is commonly used to treat hepatitis C. It is contraindicated in pregnancy, however, as animal studies have shown it to be teratogenic. It is therefore advisable that effective contraception should be used during oral administration and for 6 months after treatment[47].

Newborn vertical transmission of hepatitis C occurs in 5–10% pregnancies of HCV RNA-positive mothers. As no means of preventing vertical transmission exists, pregnancy should be planned when the viral load is

low[20]. Interferon is generally avoided in renal transplant recipients.

The outcome of pregnancies in HCV-positive women without an organ transplant is usually good, but only a few cases of pregnancy in HCV-positive renal transplant recipients have been reported[58]. In Ventura *et al.*'s report of three cases of pregnancy in HCV-positive renal transplant recipients without chronic liver disease[82], no evidence of progression of liver disease was observed during 2 years of follow-up postpartum.

ANEMIA

Anemia is commonly present in normal pregnancy. It arises because although there is an increase in red cell mass under the control of erythropoietin, the relative increase in plasma volume causes hemodilution.

Patients with solid organ transplants may become anemic as a result of this normal physiological mechanism. In addition, however, anemia may occur due to bone marrow suppression by immunosuppressive agents such as azathioprine. (MMF can also cause this but as discussed earlier is contraindicated in pregnancy.) Patients with renal transplants also may have anemia related to chronic renal impairment. This may be treated with erythropoietin prior to a pregnancy, or it may be necessary to commence treatment with erythropoietin during the pregnancy if graft function has deteriorated. It is important to consider and exclude other causes of anemia in the solid organ transplant recipient such as bleeding, hemolysis and vitamin deficiencies[83].

The general aim is to maintain the hemoglobin level at approximately 11 g/dl[58]. If the hemoglobin falls below this level, the following investigations should be considered:

- Ferritin level and transferrin saturation ratio
- Serum vitamin B12 and folate
- Hemolysis screen including blood film to look for evidence of red blood cell fragmentation
- Parvovirus infection test.

Erythropoietin can be safely used in pregnancy[84,85], as it does not appear to cross the placenta and is not reported to be teratogenic[86]. It is, however, associated with increases in blood pressure which necessitates careful monitoring. Hou recommends that erythropoietin therapy should be commenced if the hematocrit falls below 30% and the dose titrated to maintain a hemoglobin of 10–12 g/dl[20].

POST-TRANSPLANT ERYTHROCYTOSIS

Post-transplant erythrocytosis (PTE) is defined as a hematocrit of greater than 51%. It occurs in up to 20% of renal transplant recipients and is most common within the first 2 years after transplantation[58]. The etiology of PTE is unclear, but may possibly be due to the oversecretion of erythropoietin by native kidneys, transplanted kidneys or the liver. Untreated, PTE is associated with increased risk of vascular and thromboembolic disorders. ACE inhibitors or ARBs are commonly used to treat PTE, but both are contraindicated in pregnancy. Pregnant transplant recipients known to have PTE should have their hematocrit monitored regularly together with assessment of thromboembolic risk. Venesection can be considered if the hematocrit rises significantly[87].

HYPERLIPIDEMIA

Many renal transplant recipients are prescribed statin therapy to treat hypercholesterolemia and reduce the risk of cardiovascular events and morbidity[88]. Animal studies suggest that statins are teratogenic, and case reports in humans have described central nervous system defects and limb abnormalities in newborns exposed to statins *in utero*[76,89–91]. Statins

are contraindicated in pregnancy, and should be discontinued prior to conception[47,58].

SKELETAL PROBLEMS

Abnormal parathyroid hormone concentrations are seen in 77% of renal transplant recipients[92], due either to impaired transplant function or to incomplete resolution of pre-transplant hyperparathyroidism. In general hyperparathyroidism in the renal transplant patient is mild and asymptomatic, but few published data describe the outcome of pregnancy[58]. In a single case report of a renal transplant patient with mild tertiary hyperparathyroidism, albeit with a stable serum calcium level despite a deterioration in renal function, the infant developed mild neonatal hypocalcemia requiring treatment with intravenous calcium gluconate[92].

A variety of medications may be prescribed for the management of skeletal problems in renal transplant recipients, including alfacalcidol, calcium supplements, phosphate binders, bisphosphonates and, more recently, cinacalcet. These should be reviewed prior to pregnancy with a view to stopping those that are not advised in pregnancy. Calcium supplements and alfacalcidol are safe in pregnancy and can be continued. Calcium-containing phosphate binders are also safe in pregnancy, but newer agents such as lanthanum carbonate and sevelamer (Renagel) should be avoided, although evidence regarding these drugs is scant at present. Bisphosphonates, which are used in the treatment and prevention of osteoporosis, are known to cross the placenta, but very little is known about their safety in pregnancy. In general bisphosphonates should be discontinued pre-pregnancy or as soon as pregnancy is suspected, and careful consideration should be given before these agents are prescribed to women of childbearing age[58].

Table 2 summarizes which commonly used drugs in solid organ transplant recipients are considered safe in pregnancy and which are not.

Table 2 Table of drugs and their use in pregnancy

Drugs considered safe in pregnancy	*Drugs not recommended for use in pregnancy*
Immunosuppressive agents	Immunosuppressive agents
Prednisolone	Mycophenolate mofetil (MMF)
Azathioprine	Sirolimus
Cyclosporine	
Tacrolimus	Antihypertensive agents
	Angiotensin converting enzyme (ACE) inhibitors
Antihypertensive agents	Angiotensin receptor blockers (ARBs)
Methyldopa	Furosemide
Labetalol	
Calcium channel blockers	Other drugs
Hydralazine	Ganciclovir, valganciclovir
	Bisphosphonates
Other drugs	Lanthanum carbonate, sevelamer
Aspirin	Statins, e.g. atorvastatin, simvastatin
Aciclovir	Lamivudine
Alfacalcidol	Ribavarin
Calcium-containing phosphate binders	Trimethoprim

CONCLUSION

Solid organ transplantation restores fertility to many women with end-stage organ disease and undoubtedly offers the best chance of a successful pregnancy to women of childbearing age. In order to make an informed decision, it is essential that women of childbearing age are counseled regarding contraception and pregnancy, ideally prior to transplantation. Pregnancy can then be planned at an optimum time to protect graft function and minimize risks to the fetus. Medications can be modified where necessary, and concurrent medical problems such as hypertension can be identified and a management plan during pregnancy formulated. Despite all efforts, pregnancy in a solid organ transplant recipient remains high risk, and should be managed by an appropriate multidisciplinary team as described above.

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28
Gynecological malignancies

Jafaru Abu

CERVICAL CANCER

The incidence of cervical cancer in the UK and in most of the Western world has declined since the early 1980s when effective cervical cancer screening became the standard of care. In 2005, a total of 2803 cases (8.4 per 100,000) of cervical cancer were documented in the UK, representing about 2% of all female cancers, making cervical cancer the 12th most common cancer in women in the UK[1]. In the US, about 13,000 new cases are recorded every year with a rate of approximately 1 per 21,000 women and a lifetime risk of developing cervical cancer of 1 in 117[2].

Worldwide, cervical cancer remains the major cause of cancer death in women, especially in the developing world[3]. About 0.5 million new cases are seen annually and the condition causes over 0.25 million deaths every year[4]. Of such deaths 80% occur in the developing world where effective cervical cancer screening programs do not exist.

Almost all cases of cervical cancer are due to persistence of the oncogenic human papillomavirus virus (HPV) infection, a form of sexually transmitted disease. The three main risk factors for disease progression are sexual activity, smoking and immune suppression. Oncogenic HPV is detected in approximately 99.7% of all cases of cervical cancer[5–7].

Treatment of cervical cancer and impact on future pregnancy outcome

The standard treatment for cervical cancer is either radical hysterectomy with pelvic lymphadenectomy or radical chemoradiotherapy. A newer type of treatment called radical trachelectomy has recently been developed. This is a fertility sparing procedure that is only feasible for early stages of cervical cancer as described below[8].

With effective screening the majority of cervical cancer cases can be detected in the very early stages, when conservative management and fertility preservation is possible. Such fertility preserving procedures are only possible from stage 1a1 to small volume stage 1b1 disease.

Stage 1a1 disease (invades the cervical stroma to less than 3 mm deep and less than 7 mm wide)

This is the earliest form of the disease. The risk of lymph node involvement is usually less than 0.5%. The majority of cases are usually diagnosed following a large loop excision of the cervical transformation zone (LLETZ) or after a cone biopsy for a severe smear abnormality (Figures 1 and 2).

If the excision margins are clear of the disease and of cervical intraepithelial neoplasia (CIN), no further treatment is necessary apart from management with regular follow-up smears. If the excision margins are involved with CIN, then further loop excision is usually recommended after 4–6 weeks. Usually, the implication for pregnancy outcome following one loop cervical biopsy is negligible. However, after two or more loop excisions there is

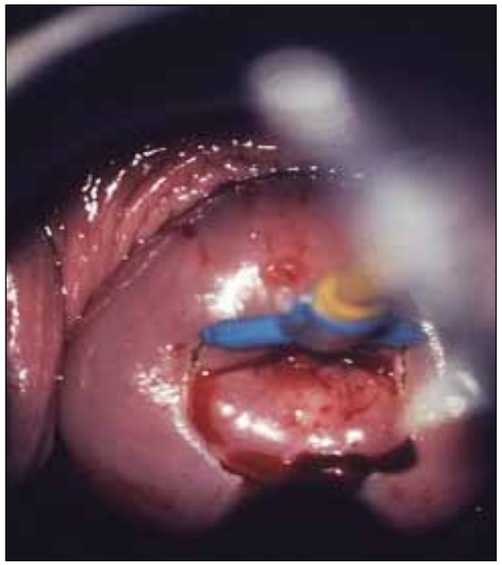

Figure 1 Loop cervical biopsy

a small but significant risk of late miscarriage and premature labor due to cervical incompetence. Therefore, women who have had two or more loop excisions should be closely monitored by an obstetrician throughout the pregnancy. In the first and second trimesters, the cervical length should be measured at regular intervals with a transvaginal ultrasound scan. The internal cervical os should also be assessed to exclude 'funneling'. If there is evidence of cervical shortening with or without 'funneling', a cervical suture may be inserted in either the late first trimester or early second trimester to prevent premature labor.

Stage 1a2 disease (invades to a depth greater than 3 mm, but less than 5 mm, with horizontal spread not exceeding 7 mm)

The risk of lymph node metastases at this stage is about 5–7.5%. No consensus exists regarding the optimal management of stage 1a2 cervical cancer. Treatment options include:

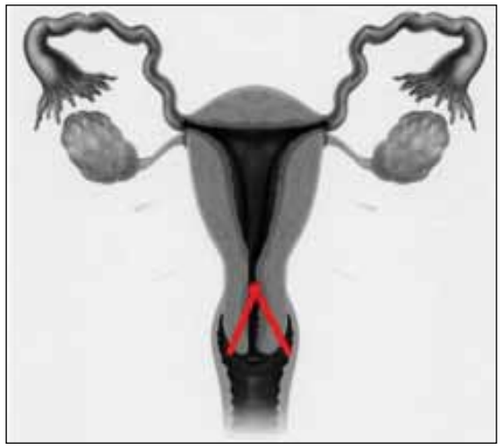

Figure 2 Diagram showing the part of cervix where a cone biopsy is performed

1. Radical hysterectomy and pelvic lymph node dissection;
2. Radical trachelectomy (Figure 3) and laparoscopic pelvic lymph node dissection;
3. Conization of the cervix followed by laparoscopic pelvic lymph node dissection.

Following radical hysterectomy, assuming pelvic irradiation is avoided, ovarian function is usually preserved thereby preventing the development of premature menopause. Where such women still desire to have children, their only option is surrogacy.

Trachelectomy and cervical conization followed by laparoscopic pelvic lymph node dissection are fertility preserving procedures in women desiring to have children. Careful preoperative counseling (as in radical hysterectomy) is required. The limitations of such a procedure and the fact that no long-term data are available regarding prolonged survival should be carefully discussed with the patient. Radical trachelectomy was first developed by Daniel Dargent as a modification of the radical vaginal hysterectomy described by Schauta[9,10]. It involves removing the cervix, parametria and a cuff of the vagina, thereby preserving

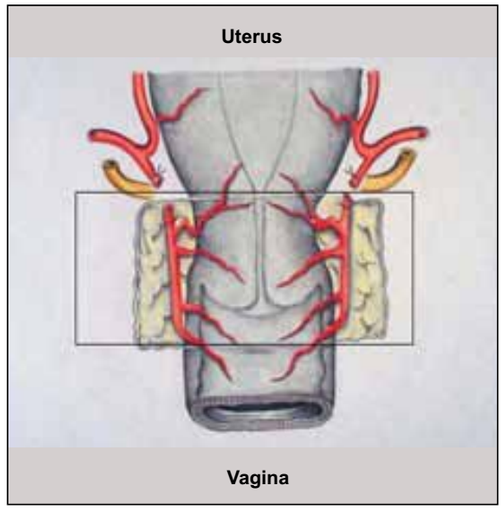

Figure 3 Diagram showing extent of tissue removal during radical trachelectomy for stage 1a2 or small volume stage 1b1 cervical cancer

the body of the uterus for fertility. The procedure is combined with either extraperitoneal or laparoscopic lymphadenectomy. Following radical trachelectomy, a cervical suture is left *in situ* and the vaginal and uterine isthmus is anastomosed, completely burying the suture. The subsequent mode of delivery will be by elective cesarean section. The pregnancy rate amongst women trying to conceive following radical trachelectomy ranges between 53% and 70% within 5 years of trying[8]. Only about half of such pregnancies are carried to term. Approximately 13% are lost in the early second trimester, whilst the rest are usually delivered prematurely due to the presence of an incompetent cervix. Stenosis can also be a major problem following radical trachelectomy, causing menstrual disorders or fertility problems. The majority of such problems are usually resolved following cervical dilatation. On the other hand, if patients succeed in conceiving, they should be warned about the risk of second trimester miscarriage or of premature labor. Close obstetric follow-up throughout the pregnancy is required with careful transvaginal ultrasound monitoring of the cervix.

Small volume stage 1b1 cervical cancer (lesions confined to the cervix more than stage 1a2 but not greater than 2 cm)

For women in the reproductive age group, treatment options are either radical hysterectomy and bilateral pelvic lymphadenectomy or radical trachelectomy followed by laparoscopic pelvic lymphadenectomy[11]. The latter option is recommended for women desiring fertility preservation. However, after radical trachelectomy, the following problems may arise and patients should be counseled beforehand that extra postoperative vigilance will be necessary:

1. Cervical stenosis;
2. Cervical incompetence;
3. Infertility;
4. Difficulty obtaining adequate follow-up cervical smears.

ENDOMETRIAL CANCER

The incidence of endometrial cancer (Figure 4) has gradually increased over the past decade. For example, in 2005 endometrial cancer was the most common gynecological cancer in the UK, accounting for 6891 cases and 1651 deaths[1]; in the US, more than 40,000 new cases and 7470 deaths were recorded in 2004[2]; Canada reported 3800 new cases in 2004[12]; and the annual incidence in Australia is about 1400 new cases[13].

About 70% of cases present with stage 1 disease and treatment with total hysterectomy and bilateral salpingo-oophorectomy provides a cure, so that the overall 5-year survival is about 75%. The majority of cases also present with well or moderately differentiated endometroid type adenocarcinoma which has a good prognosis. Although endometrial cancer

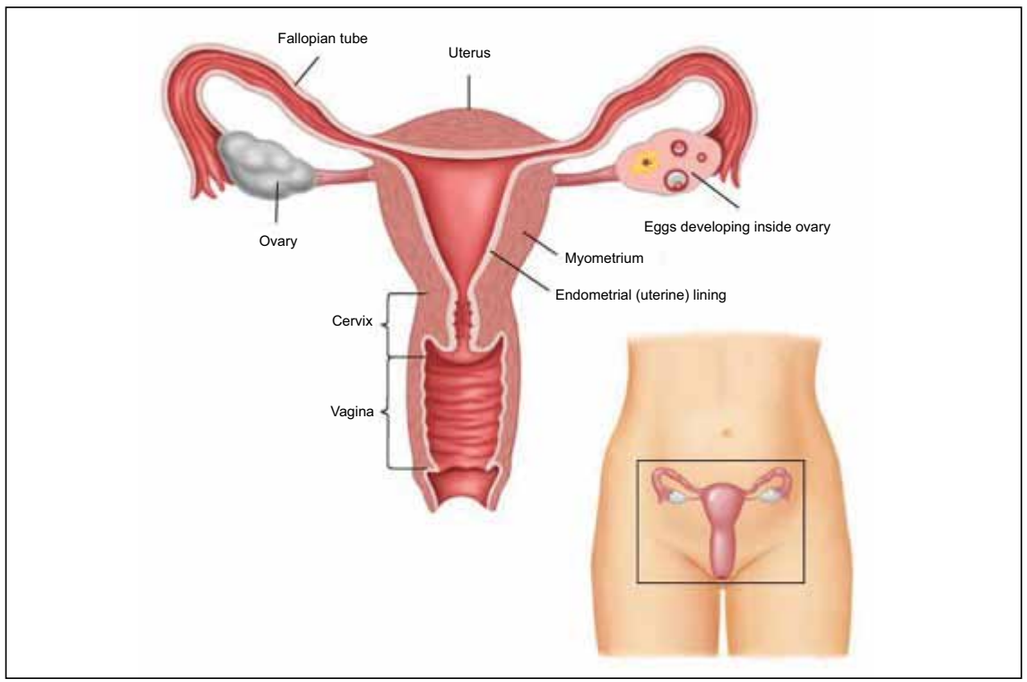

Figure 4 Diagramatic representation of the female anatomy, showing the uterine cavity, cervix and vagina and the position of the tubes and ovaries

is more commonly a disease of postmenopausal women (usually above the age of 60 years), it has been reported in younger women below the age of 45 years and therefore in the reproductive age group. The risk factors for endometrial cancer in premenopausal women include:

1. Polycystic ovarian syndrome;
2. Obesity;
3. Nulliparity;
4. Familial (hereditary non-polyposis colorectal cancer syndrome or the Lynch syndrome);
5. Estrogen secreting tumors.

In hereditary non-polyposis coli, a mismatch repair gene defect increases the risk of endometrial cancer to almost 60%.

Management of endometrial cancer in young women

About 3–14% of all endometrial cancers are diagnosed in women younger than 40 years[14]. The majority of such cases are usually associated with good prognostic features such as degree of differentiation (usually well differentiated), and focal with minimal or no myometrial invasion. Whereas the ideal management of endometrial cancer at any age is total hysterectomy and bilateral salpingo-oophorectomy with or without pelvic/para-aortic lymph node dissection, there are reports of conservative management of very early stage endometrial cancer in young women desiring to preserve fertility[15,16]. It is axiomatic that such women desiring to retain their uterus and ovaries must be properly counseled by both a gynecological oncologist and gynecological oncology

nurse specialist. This decision should not be taken lightly as the long-term implications of such an action remain to be determined.

Prior to instituting conservative management, adequate assessment of the uterine cavity should be carried out with a hysteroscope. This should then be followed by magnetic resonance imaging (MRI) staging assessing the presence or absence of myometrial invasion. Ovarian assessment should also be made using transvaginal ultrasound with or without Doppler studies. Immunohistochemistry studies should be performed on the specimen to determine the hormone receptor status, as progestin sensitivity or uptake is associated with good prognostic outcome. Progestogens have been a mainstay of therapy for women who refuse the standard treatment; although no single protocol represents the standard of care. The overall complete response rate has been reported to be in the region of about 70%[16–19]. The author's suggested treatment protocol is 160 mg of medroxyprogesterone acetate (Megace) orally daily for 90 days followed by further hysteroscopy and endometrial samplings. If there is evidence of complete response (that is absence of tumor in all biopsies), treatment is continued for a further 90 days and then stopped.

The patient is then seen on a 3-monthly basis and undergoes outpatient pipelle endometrial sampling every 6 months indefinitely except if pregnant. On completion of family, or if the patient no longer wishes to have a family, total laparoscopic hysterectomy and bilateral salpingo-oophorectomy should be advised. Some have quoted a pregnancy rate as high as 58% following treatment with progestogens. For those women who do not desire to get pregnant immediately, long-term maintenance therapy with either the combined oral contraceptive pill or the levonorgestrel intrauterine system (Mirena) may be appropriate. Such treatment is discontinued as soon as the patient wishes to conceive.

Another issue that has recently come to the fore is the possibility of ovarian conservation in very young women with early stage endometrial cancer who consent to hysterectomy. If the ovaries are conserved, this would invariably give the patients the option of surrogacy in the future if they so desire. Ovarian conservation would also prevent the devastating effects of menopausal symptoms and estrogen deprivation, in particular osteoporosis. It is important to recognize, however, that approximately 25% of endometrial cancer patients will have coexistent ovarian cancer (either metastatic or primary disease). Under these circumstances, it is vital to discuss ovarian conservation with the patient before her surgery or conservative medical management.

The management of atypical endometrial hyperplasia

Atypical endometrial hyperplasia is characterized by excessive proliferation of endometrial cells associated with cellular stratification, densely eosinophilic cytoplasm, tufting, loss of nuclear polarity, and enlarged and prominent nuclei with increased evidence of mitosis[20]. These nuclear features are more or less similar to what one finds in true cancer cells except that there is no evidence of invasion. The etiological factors are similar to those for endometrial cancer, and young women who are obese and have polycystic ovarian syndrome are particularly affected. The drive for endometrial stimulation is excessive estrogen.

Several studies have shown that complex hyperplasia with atypia has a 30–50% risk of progression to frankly invasive carcinoma if left untreated[21]. The risk of concurrent endometrial cancer at the time of diagnosis varies from as little as 17% to almost 52%. Thus, the recommended treatment standard is total hysterectomy and bilateral salpingo-oophorectomy. However, fertility preservation may represent a huge issue for young women

who have not had children. Once again, hormone treatment, as discussed above, may be a good compromise treatment in this group of patients.

OVARIAN CANCER

Ovarian cancer (Figures 4 and 5) was the second most common gynecological cancer in the UK with a total of 6806 cases in 2005, and 4407 deaths in 2006[1]. In the US, there were 20,095 new cases of ovarian cancer in 2004 and 21,650 cases in 2008; the condition was responsible for 15,520 deaths in 2008[22]. Given these numbers, ovarian cancer causes more deaths than any other cancer of the female reproductive tract. As the symptoms and signs are usually highly non-specific, about 75% of patients present with advanced stage disease where surgery alone is no longer curative. When diagnosed in very early stages, however, treatment is usually very effective. Although the symptoms and signs (such as abdominal swelling, urinary frequency, abdominal pain and alteration in bowel habits) are not specific, it is important to remember that ovarian cancer does cause symptoms and signs. Thus, the notion that ovarian cancer is an absolutely 'silent killer' should be discarded. It is important for every woman to know her body very well and also to know what is normal for her. Indeed, it is important for health care providers to encourage women to become more aware of themselves and their daily functions so that they can notice subtle alterations when they appear. At the same time, clinicians should have a high index of suspicion and should not ignore the so-called 'non-specific' symptoms, especially when they appear in women who have presented without symptoms for years and now complain for the first time. Clinicians should learn to listen more to women when they complain of any of the above symptoms. This means not just to sit across from the patient and let her talk but to follow-up with suitable questions which will illuminate the onset, nature and extent of the symptoms, especially in those who have not been known to complain of anything in the past.

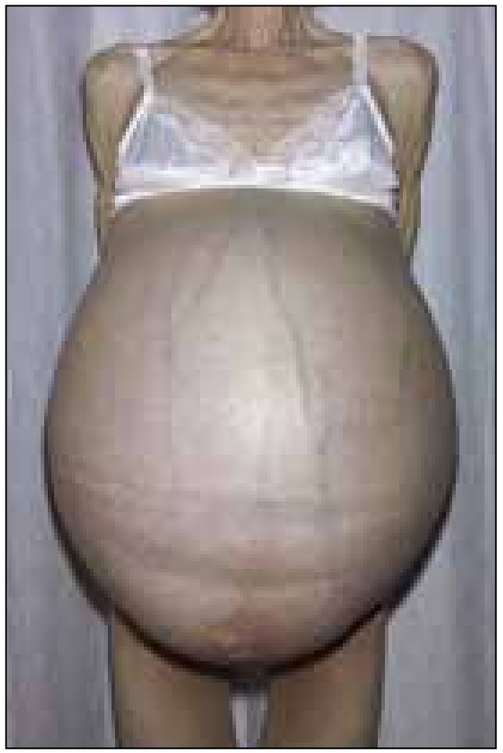

Figure 5 Ovarian tumor and ascites causing markedly distended abdomen with prominent veins, evidence of weight loss and stretched out skin

Ovarian cancer is a disease of older women, and approximately 90% of cases occur in women older than 40 years, with the majority usually above the age of 55 years. Women are only more likely to have ovarian cancer at an earlier age if they are at a high risk, such as having a family history of ovarian or breast cancer and if they are nulliparous. The combined oral contraceptive pill appears to offer some degree of protection against the development of ovarian cancer.

The three main types of ovarian cancer are:

1. Epithelial ovarian tumors – derived from the surface epithelium of the ovary;
2. Germ cell ovarian tumors – derived from the egg (ovum) producing part of the ovary (not all germ cell tumors are malignant);
3. Ovarian stroma tumors – derived from the connecting tissue elements of the ovary.

Epithelial ovarian tumors

Benign epithelial ovarian tumors

The majority of epithelial ovarian cancers are benign, which means they lack cellular atypia and invasive characteristics. Such benign epithelial tumors are serous or mucinous adenomas and Brenner tumors. Therefore, they require conservative management in the young woman with reproductive potential. Unilateral salpingo-oophorectomy or even ovarian cystectomy is all that is required. Such procedures can be undertaken with minimally invasive techniques without need for major laparotomy incisions. The vast majority of these tumors are only diagnosed in postoperative specimens. However, careful preoperative investigations with imaging (ultrasound, computed tomography (CT) or MRI) and tumor markers should lead to a high index of suspicion. Therefore, conservative management can be offered to women desiring to preserve their fertility.

Epithelial ovarian tumors of low malignant potential (borderline ovarian tumors)

These types of epithelial ovarian tumors differ from the typical cancerous ovarian tumors because they appear not to invade the ovarian stroma. They account for about 10–15% of all epithelial ovarian tumors and are usually very slow growing tumors. The majority are diagnosed in the early stages. Even in advanced stages, with spread into the peritoneum or omentum, they usually produce characteristic 'non-invasive' implants. Unlike the frankly invasive epithelial ovarian tumors which affect mainly postmenopausal women, they tend to affect the younger age group of women and those in the reproductive age.

When a complex ovarian mass is found in a young woman of reproductive age, as with any other age, preoperative investigations such as tumor markers (CA125, CEA, β-human chorionic gonadotropin (hCG), α-fetoprotein (AFP)) should be checked and appropriate preoperative imaging should be carried out with ultrasound with or without Doppler imaging, CT scan or MRI. Unfortunately, tumor markers, especially CA125, have been of no value in either the preoperative management or the follow-up of women with borderline ovarian tumors.

Women should be properly counseled prior to surgery. The ideal treatment, even if borderline ovarian tumor is suspected, is total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy. In some cases where there are obvious implants within the peritoneal cavity, these should be excised. The aim should be complete surgical debulking. There may be an argument for pelvic and para-aortic lymphadenectomy for complete tumor staging. However, in young women desiring to preserve their fertility, and when the tumor is unilateral, it may be feasible to carry out conservative surgery such as unilateral salpingo-oophorectomy with the rest of the staging procedures as above. Salpingo-oophorectomy is preferred to cystectomy even if the disease is confined to one ovary, as this is less likely to be associated with risk of recurrence[23]. Cystectomy is more likely to be associated with intraoperative surgical rupture, thus increasing the risk of recurrence. If the contralateral ovary looks normal, there may be no need to biopsy it. On the other hand, if it looks cystic and/or abnormal, a frozen section biopsy should be obtained. If the whole of the ovarian tissue is uninvolved, it may still be

feasible to preserve some of the ovarian tissue. Even if there is the need to remove the contralateral tube and ovary, the uterus does not necessarily need to be removed. This would offer the woman the choice of egg donation and *in vitro* fertilization later in life. Hormone replacement is recommended following bilateral salpingo-oophorectomy to both maintain the endometrium and prevent menopausal symptoms and osteoporosis due to estrogen insufficiency.

Following conservative surgery for borderline ovarian tumors, the patient should be closely followed up at 3-monthly intervals in the first 2 years with 6-monthly pelvic ultrasound scans. Thereafter, she should be followed up 6-monthly with yearly ultrasound scans for a total follow-up period of 10 years, except if she opts for a full hysterectomy and removal of the remaining ovary and tube having completed her family. The place of CA125 monitoring at follow-up is controversial, and the author's personal preference is to only do this in women who have previously had elevated CA125 prior to surgical management.

It is rational to ask if there is a role for adjuvant chemotherapy in borderline ovarian tumors. This remains controversial. No arguments surround the fact that complete surgical debulking should be the goal in both early and advanced stage disease. The overall 5-year survival for women with stage 1 and 2 disease is greater than 90%. Some authors have used chemotherapy for advanced stage disease with invasive implants and have reported varied results. Chemotherapy does not appear to improve the overall survival for disease with non-invasive implants in either the peritoneum or the omentum.

Invasive epithelial ovarian tumors

Epithelial ovarian cancer is relatively uncommon in women below the age of 50 years and even more so below the age of 40 years. Most women have completed their family before the age of 40 years. The management of epithelial ovarian cancer in women who wish to preserve their fertility depends on the stage of the disease. Ideally, following routine preoperative investigations, all women with ovarian cancer should undergo complete surgical staging which includes total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy with pelvic and para-aortic lymphadenectomy. Longer-term survival correlates positively with absence of residual disease following surgery (optimal cytoreductive surgery), younger age of the patient, favorable histological type (apart from serous or clear cell type), early stage disease and good performance status. Conservative management may be considered in younger women with stage 1 disease and favorable histological type as detailed below. Fertility preservation is usually not advisable in women with stage 2 and above irrespective of the histological type.

Stage 1a disease (confined to one ovary without involvement of the surface of the ovary and no ascites) Management of stage 1a disease is by laparotomy via a midline incision to allow complete inspection of the upper abdomen. Peritoneal washings are obtained for cytology, and a unilateral salpingo-oophorectomy and omentectomy are performed. Para-aortic lymph node dissection is also performed to assist in optimal staging.

Stage 1b disease (involvement of both ovaries, but no tumor on the surface of the ovary and no ascites) Management of stage 1b disease is again by laparotomy, peritoneal washings for cytology, bilateral salpingo-oophorectomy, omentectomy and para-aortic lymphadenectomy. The uterus is preserved as this would give the woman the option of egg donation for *in vitro* fertilization. Hormone replacement should be prescribed to maintain endometrial integrity as well as to prevent menopausal symptoms and osteoporosis.

Stage 1c disease (stage 1a or 1b plus one or more of the following – tumor on the surface of the ovary, positive peritoneal cytology or surgical rupture of the cyst) Surgical management for stage 1c disease is as for stage 1a or 1b above but with the addition of adjuvant chemotherapy (single agent platinum or platinum based combination). Once again, in younger women, hormone replacement is usually recommended for the reasons given above.

Germ cell ovarian tumors

These are rare of gynecological tumors. Ovarian germ cell tumors represent about 25% of all germ cell tumors. Other sites where germ cell tumors can be found include the testicle (12%), sacrococcygeal region (40%), brain (5%), and neck and thorax (18%). Not all ovarian germ cell tumors are malignant. The main histological types of ovarian germ cell tumors are the mature teratoma or dermoid cyst which is usually benign, the immature teratoma which is malignant, yolk sac tumors, dysgerminoma, choriocarcinoma, embryonal carcinoma, endodermal sinus tumors and mixed germ cell tumors.

Ovarian germ cell tumors usually affect one ovary and are more likely to be found in girls and women below the age of 40 years. Very rarely, they may also be found in children and elderly women. The symptoms are a feeling of pelvic-abdominal fullness or bloating, abdominal pain, occasional irregular bleeding and urinary frequency due to pressure on the urinary bladder. It is therefore important to have a high index of suspicion as some of these symptoms are non-specific. Abdominal and pelvic examination may reveal a pelvic mass. A pelvic ultrasound would show a complex ovarian mass which is usually unilateral. Blood should be taken for the two main tumor markers, βhCG and AFP. These are very sensitive tumor markers which are usually elevated and are good indicators of complete tumor resection following surgery or response to chemotherapy. They are also very useful for subsequent follow-up after a successful treatment. Pretreatment CT scan of the abdomen, chest and pelvis provides additional evaluation of disease extent (involvement of the omentum or the para-aortic lymph nodes).

Over the past two decades, treatment of ovarian germ cell tumors has improved significantly, and it is now possible to cure most cases in even advanced stage disease. In young women desiring fertility preservation and with stage 1 and 2 disease, unilateral salpingo-oophorectomy should be considered at laparotomy and with full surgical staging. Surgery is usually curative with stage 1 disease. In stage 2 and above, apart from ovarian dysgerminoma where radiotherapy might be considered, combination chemotherapy consisting of cisplatin, etopoxide and bleomycin is usually very effective. Following cessation of chemotherapy, ovarian functioning usually returns over a period of 3–6 months. Other combination chemotherapy has also been used. The use of radiotherapy, however, for advanced stage dysgerminoma would lead to ovarian failure and loss of fertility.

Ovarian stromal (or sex-cord stromal) tumors

These are tumors derived from the connective tissue elements of the ovary. They are rare and account for about 5–10% of all types of ovarian cancers. They occur more often in young girls and women of reproductive age, and only about 10% occur in women above the age of 50 years. Tumors derived from the ovarian stroma may be associated with abnormal production of the sex steroid hormones (progesterone, estrogen, testosterone, androstenedione, dehydroepiandrosterone). The feminizing hormones (progesterone and estrogen) can cause abnormal uterine bleeding or precocious puberty if the tumor develops in children. The

male sex hormones, on the other hand, can cause virilization, hirsutism, greasy skin and infertility.

The most common types are granulosa cell tumor and Sertoli-Leydig tumors. Other types of ovarian stromal tumors include theca cell tumor, fibroma, thecoma, lipid cell tumor and gynandroblastoma. The vast majority of ovarian stromal tumors (approximately 75%) will present with stage 1 disease. Their earlier presentation, unlike their epithelial counterparts, is probably because of the associated symptoms secondary to abnormal hormone production.

Granulosa cell tumors

These tumors account for only about 2% of all ovarian malignancies and usually present early, most typically as complex unilateral ovarian tumors on ultrasound or CT scan. Because of the abnormal hormone production, they may be associated with abnormal uterine bleeding or endometrial hyperplasia. Apart from estrogen, they also produce inhibin, which is a useful tumor marker in subsequent follow-up. Surgery alone is usually curative. Because these tumors tend to present early, unilateral salpingo-oophorectomy and omentectomy with preservation of the contralateral ovary and uterus is all that is required. In advanced stage disease, total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and surgical debulking of all macroscopic tumor deposits is the aim, because there is no evidence of clear benefit from chemotherapy and radiotherapy in granulosa cell tumor.

Sertoli-Leydig tumors

These tumors account for only 0.5% of all ovarian cancers. By producing male hormones, they can cause virilization and hirsutism. Other symptoms include oligomenorrhea, amenorrhea and infertility. They are a rare cause of precocious puberty in children and infants. About 97% of cases present as stage 1 disease when conservative surgery and fertility preservation would be most appropriate.

VULVAR CANCER

Vulvar cancer is very rare in women in the reproductive age group with only a handful of cases reported in women below the age of 40 years. The majority of cases present as early stage disease where a more conservative approach to management is feasible. Wide local excision of the primary tumor, without the need for radical vulvectomy is all that is usually required. This may be combined with unilateral or bilateral groin node dissection depending on the depth of invasion or the location of the primary tumor in the vulva. With tumor depths greater than 2 mm, groin node dissection is usually recommended. If it is a lateralized disease, then unilateral groin node dissection is performed, and the contralateral groin is preserved except if there is evidence of metastasis in the dissected groin nodes. Nowadays, women with small volume disease can be offered the lesser surgical option of sentinel lymph node dissection of the groin. This is a far less morbid surgical option without the need for extensive groin node dissection.

Wide local excision of the vulvar primary tumor would in most cases preserve the anatomy of the external vulva. Plastic reconstruction may be required to restore any anatomical anomaly, if it should appear postsurgery. In young women still desiring fertility, subsequent deliveries should be by cesarean section as the vulva, although adequate for sexual intercourse, may be too tight for vaginal deliveries. The woman should be appropriately counseled and delivery options carefully explored ideally in the preconceptional period or in the early stages of pregnancy.

Adjuvant radiotherapy is only indicated in women with very close tumor excision margins or involved groin nodes. In those with very close tumor resection margins, the option of further wide local excision should always be considered before resorting to adjuvant radiotherapy. In women requiring groin irradiation, the patient must deal with the risk of irradiating the pelvis as well as with the potential of ovarian tissue damage which can lead to premature menopause. This would, of course, have implications for fertility in women of reproductive age group.

PRECONCEPTION FERTILITY PRESERVATION IN GYNECOLOGICAL ONCOLOGY

So far, we have mentioned radical trachelectomy as a fertility preserving surgical option in the management of the young patient with early stage cervical cancer and conservative management in some women with either early stage endometrial cancer or atypical endometrial hyperplasia after appropriate counseling. However, following the diagnosis of cancer in young women within the reproductive age range, ovarian function is a major issue that merits discussion with the patient and her significant other or family, as appropriate. This is even more necessary if treatment involves radiotherapy and chemotherapy. Radiotherapy treatment, especially external beam irradiation, will most certainly destroy ovarian function, rendering premenopausal women menopausal. Fortunately, major developments in reproductive medicine over the past two decades make it possible to offer women desiring to conceive after cancer treatment options such as:

1. Egg preservation or freezing;
2. Embryo freezing;
3. Ovarian freezing.

Whilst it is important to discuss these options and their relative degrees of success, it is also important for the clinician to consider the overall disease survival and life expectancy of the patient. It may not be ethically justifiable to offer these options to patients with an advanced stage disease where cure rate might be very low. Of the above three options, embryo freezing appears to carry most success and should be the preferred option in women who are in a stable relationship. Until recently, egg preservation or freezing was still experimental; however, it is now increasingly being offered as a realistic option to women in the US and in many European countries. Ovarian freezing is still experimental and reported success rates are low at the time of writing.

Recently, there have been sporadic case reports on whole ovary transplantation and some successes have been reported in identical twins with premature ovarian failure not secondary to cancer or cancer treatment. The technique of transplantation of previously stored ovarian tissue to the same woman has also been reported in the past several years. However, the technique of whole ovary transplantation is totally a new concept. As with any other organ transplantation, the risks of immunosuppression and rejection should be carefully examined. The opinion of the author is that whole ovary transplantation should only be carried out in expert centers and under the auspices of research. Other fertility options are available and should also be considered, including surrogacy and adoption.

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29

Preparing for a pregnancy after bariatric surgery

Michelle A. Kominiarek

INTRODUCTION

Obesity and its associated co-morbidities are now considered epidemic in many parts of the world[1]. In the United States, 68% of the population were either overweight or obese in 2007–2008; of these individuals, obesity was more often present in women compared to men[2]. Without doubt, obesity is a complex chronic disease to which adding a pregnancy further complicates management and perinatal outcomes. For example, obese patients are more likely to have an infant with birth defects, subsequently develop diabetes or hypertension, have a stillbirth, or require cesarean delivery[3–8]. In addition, labor is prolonged, and operative complications including infections, hemorrhage and increased operating times are common[9–11].

Of all treatments currently available for obesity (diet, behavioral changes, exercise, pharmacotherapy, surgery), bariatric or weight loss surgery offers the greatest chance for success in the morbidly obese[12,13]. Moreover, bariatric surgery can resolve or improve co-morbidities such as hypertension and diabetes. Candidates for bariatric surgery are those with a body mass index (BMI) more than 40 kg/m^2 or more than 35 kg/m^2 with co-morbidities such as cardiovascular disease, diabetes, or sleep apnea. The three major types of bariatric surgery – restrictive, malabsorptive and mixed procedures – are named by the mechanism by which weight loss occurs. The specific type of surgery performed is individualized and also varies depending on hospital resources and physician expertise. However, the most common surgeries performed at present are the Roux-en-Y gastric bypass (RYGB, mixed procedure) and laparoscopic adjustable gastric banding (LAGB, restrictive procedure)[14,15]. Reflective of the growing problem and its importance to the general health of the public, the number of bariatric procedures performed increased from less than 20,000 in 1995 to more than 200,000 in 2006[16].

Of interest to clinicians focusing on women's health is that the majority of reproductive age patients (18–45 years) having bariatric surgery are female (83%)[17]. In general, pregnancies occurring after bariatric surgery have favorable outcomes[17,18], and studies suggest that co-morbidities such as diabetes and hypertensive disorders often are improved[19,20]. It is important to note that birth defects and perinatal mortality are not increased[18,21,22]. However, evidenced-based research on pregnancy outcomes after bariatric surgery is lacking, as the majority of studies are retrospective (case–control or cohort) with small numbers of patients. Nevertheless, *the keys to improving perinatal outcomes after bariatric surgery are appropriate pregnancy planning and optimizing nutrition and weight status prior to pregnancy.* This chapter addresses issues that occur in reproductive age women either planning a pregnancy or pregnant after bariatric surgery.

FERTILITY

Infertility is only one of the many co-morbidities associated with obesity, with a diagnosis frequently occurring prior to bariatric surgery or weight loss. For example, in the Longitudinal Assessment of Bariatric Surgery Survey, 42% of women who tried to become pregnant prior to bariatric surgery had experienced infertility[23]. The pathophysiology behind the relationship between obesity and infertility frequently includes insulin resistance and hyperinsulinemia, altered pulsatile gonadotropin secretion, elevated leptin levels and diminished ovarian reserve[24]. Infertility in obese women is commonly related to ovulatory dysfunction, including syndromes such as polycystic ovarian syndrome. After bariatric surgery, menstrual cycle irregularities and hyperandrogenism improve[25–28]. Indeed, several reports have observed improved fertility and/or unanticipated pregnancies after bariatric surgery, especially in adolescents[26,29–32].

Despite this, future fertility may not be important to all women having bariatric surgery. Although 50% of reproductive aged women planning to have bariatric surgery would never try to become pregnant after their operations, 30% reported that a future pregnancy was important[23]. Therefore, it is important for practitioners to counsel patients *preoperatively* about reproductive changes that can occur after weight loss from bariatric surgery and to discuss contraception with all women of reproductive age regardless of whether they desire a future pregnancy. An important part of optimal care after bariatric surgery is preventing an unintentional conception postoperatively.

Contraceptive counseling is challenging in the presence of medical conditions such as obesity. Furthermore, a few studies have raised concerns over the effectiveness of oral contraception after bariatric surgery[33–36]. However, some of these reports evaluated pregnancy outcomes after purely malabsorptive procedures such as the jejunal–ileal bypass which is no longer performed[35]. Gerrits *et al*. described 40 patients who had a malabsorptive procedure whereby two of nine women using oral contraception became pregnant in the first year[33]. Contraception failure was attributed to malabsorptive complications (patients were experiencing diarrhea, steatorrhea and vomiting concomitantly) and not to non-compliance. Another theoretical concern is use of depot medroxyprogesterone acetate (DMPA) and its effects on bone mineral density. Bone loss can occur after bariatric surgery because of vitamin deficiencies, especially in association with malabsorption. Given that patients may still be obese after bariatric surgery, this also needs to be considered in planning contraception[37]. Unfortunately, limited evidence is available regarding the use, effectiveness and safety of contraception after bariatric surgery, but it is unlikely that there is a significant decrease in efficacy for oral contraceptive pills[38]. Long-acting reversible methods (i.e. intrauterine device, DMPA, or implantable contraception) are highly efficacious and avoid the risk of venous thromboembolism, which is an important consideration if the patient is still obese.

TIMING CONCEPTION AFTER BARIATRIC SURGERY

The first 18 months after bariatric surgery are characterized by rapid weight loss. Because of this, concerns have arisen that fetal nutrition would be compromised if pregnancy occurred immediately after surgery; these concerns have been followed by recommendations to wait 12–24 months prior to conceiving after bariatric surgery[39]. However, one potential disadvantage to delaying pregnancy is the decreasing likelihood of conception with advancing maternal age. According to insurance claims data from 2002 to 2006, the median time at which women delivered after surgery was

19.6 months (mean 20.9 months, standard deviation 10.3 months and interquartile range 13.1–27.2 months)[20]. This finding suggests that many women conceived less than a year after surgery, but whether these gestations were planned or unplanned is not known.

A few studies have compared pregnancies occurring early (<12–18 months) vs. late (>18 or >24 months) after bariatric surgery. Similar outcomes were found with respect to infant birth weights, congenital anomalies and cesarean delivery rates[40–43]. In Dao's report of 21 pregnancies within 1 year of surgery and 13 pregnancies after the first year of surgery, maternal weight changes varied from weight loss (range −70 to +45 pounds, mean +4 pounds) in the pregnancies occurring early after surgery group, to excessive weight gains (13–75 pounds, mean 34 pounds) in the pregnancies occurring later. Weight gain during pregnancy may predict long-term weight status; however, studies on the impact of early vs. late pregnancy and long-term maternal outcomes such as weight loss success and development of co-morbidities are rare. The purpose of one study was to compare the need for additional surgery for a complication after a LAGB in those with and without a subsequent pregnancy. This included either band revision secondary to a complication, such as a proximal pouch dilation or band erosion, or a port complication[44]. Band revisions and weight loss (48% of excess weight lost in both groups, $p = 0.74$) were not different between the groups at 2 or 3 years after a pregnancy. However, the time between the initial LAGB operation and pregnancy was shorter for those women who required primary revisions for band complications compared to those who did not require revisions within 3 years of pregnancy (2.2 vs. 3.1 years after LAGB, $p = 0.03$). The authors of this report concluded that pregnancy probably does not have an effect on the rate of band revisions; however, a shorter period between LAGB placement and pregnancy may increase the need for further surgery to treat a band complication. No study to date has compared the impact of early vs. late pregnancy on infant and adolescent outcomes.

Haward *et al*. do not advise their patients to wait to conceive after LAGB procedures, because nutritional deficiencies are rare compared to RYGB[44], and these authors further acknowledge that delaying a pregnancy for 2 years may not be practical for all patients. Regardless, other issues must be considered in the first year after bariatric surgery, including adjusting to a new dietary regimen and a new body image as well as difficulty in distinguishing postsurgical symptoms from changes that occur commonly in pregnancy (i.e. nausea). All things being considered, consensus suggests that conception should be delayed 12–18 months after bariatric surgery to minimize complications from nutritional deficiencies and promote optimal and stable maternal weight loss[39]. In the event that an early pregnancy does occur, patients can be counseled that overall the outcomes are reassuring, based on the few published studies to date.

PLANNING A PREGNANCY

Multidisciplinary approach

Obesity, like diabetes and hypertension, is a chronic disease in which weight management is complex and challenging. As such, a multidisciplinary approach contributes to successful outcomes after bariatric surgery. A comprehensive team of health care professionals (bariatric surgeons, dieticians/nutritionists, obesity specialists and psychiatrists) should be involved in the care of the bariatric patient in both the pre- and postoperative stages. This approach should also continue during preconception and pregnancy. According to published guidelines, follow-up with team members should occur every 3 months in the first year and then yearly after a LAGB[45]. After a RYGB, follow-up should occur every 3 months in the

first year, every 6 months in the second year, and then yearly[45]. Ongoing consultation with a nutritionist is especially important to maintain healthy eating behaviors and overcome additional challenges if pregnancy is desired or occurs. Additionally, patients should also obtain a consultation from a maternal–fetal medicine specialist prior to conception to discuss the potential alterations in prenatal care and perinatal outcomes in a pregnancy after bariatric surgery.

Optimizing nutrition

Optimizing nutrition is undoubtedly one of the most important aspects of planning of pregnancy after bariatric surgery. In addition to following an appropriate diet, measuring vitamin and mineral levels, and supplementing with appropriate dietary additives can help this process. Malabsorptive procedures limit nutrient absorption by bypassing sections of the small intestine. Since purely malabsorptive surgeries are rarely performed today, it now is uncommon to see protein deficiency after bariatric procedures. The RYGB creates a small gastric pouch (restrictive portion) that empties into the distal jejunum, bypassing portions of the stomach, duodenum and portions of the jejunum (malabsorptive portion). Micronutrient (folate, vitamins D and B12, calcium, iron and copper) deficiencies are more common among mixed procedures than restrictive procedures such as the LAGB. In the LAGB, a fluid-filled band is placed around the stomach just below the gastroesophageal junction, thus reducing stomach volume. *All patients are advised to take daily vitamin and mineral supplements after bariatric surgery, regardless of the type of procedure. These supplements are usually sufficient to maintain normal levels and avoid deficiencies*. This prescriptive advice is lifetime in duration. It is important to remember, however, that deficiencies still can occur as a result of decreased intake and/or intolerance to certain foods or malabsorption from the bypass of important small bowel segments. Unfortunately, only 14–59% of all bariatric surgery patients continue to take the multivitamin supplement long term[46,47]. As such, early identification, appropriate treatment and routine prophylactic supplementation of deficiencies are important in the successful short- and long-term management of bariatric surgery patients. To date, recommendations for vitamin testing and treatment published for non-pregnant patients are based on expert opinion and observational research rather than evidence from trials.

The specter of specific deficiencies is increasingly important when preparing for pregnancy, and appropriate folic acid and vitamin B12 intake during the preconception period and early gestation is crucial as is noted in Chapter 22 in order to prevent spina bifida and other birth defects[48]. The same can be said for iron deficiency anemia which can be associated with preterm delivery and low infant birth weight[49]. Laboratory testing for patients after a RYGB includes a complete blood count, electrolytes, glucose, iron studies, ferritin, vitamin B12, folate and 25-hydroxyvitamin D[50]. If the vitamin D level is low, then parathyroid hormone levels should be investigated as well. Table 1 suggests an approach to treat deficiencies both prior to and during pregnancy in patients who have had bariatric surgery. Levels have been modified from studies pertaining to non-pregnant patients[50]. It should be noted that only one daily multivitamin is recommended during pregnancy to avoid excessive vitamin A doses that may occur with two daily multivitamins. In pregnancy, a minimum of 60 g of protein per day is recommended regardless of the type of bariatric surgery. Interested readers should consult Chapter 22 for a more complete discussion of supplementation in pregnancy and the preconception period.

Special considerations

Some of the common and expected physiological and anatomical changes of pregnancy include more frequent emesis and displacement of abdominal organs. These possibilities prompt specialized pregnancy management after LAGB, also called active management of the band[31,44,46,51,52]. Adjusting the amount of fluid in the band (the maximum capacity of the band is approximately 10–14 ml) can either narrow or widen the gastric opening thus affecting caloric intake and absorption. One difference noted in these studies was that excessive weight gains occurred in those who had all the fluid removed from the band (had the band completely deflated) during the pregnancy compared to those that retained some or all of the fluid. There is no optimal means to manage bands during pregnancy, so therapy is individualized in consultation with a bariatric surgeon.

Table 1 Routine nutrient supplementation after bariatric surgery

*Non-pregnant population**	*During pregnancy*
Multivitamin 1–2 daily	One prenatal vitamin daily
Calcium citrate (1200–2000 mg/day) with vitamin D (400–800 U/day)	Calcium citrate (1200 mg/day) with vitamin D (400–800 U/day)
Folic acid 400 μg/day in multivitamin	Folic acid 400 μg/day in prenatal vitamin, replace with additional doses if deficiency confirmed
Elemental iron with vitamin C (40–65 mg/day)	Elemental iron (40–65 mg/day) plus prenatal vitamin, replace with additional doses if deficiency confirmed
Vitamin B12 ≥350 μg/day orally or 1000 μg/month intramuscularly or 3000 μg every 6 months intramuscularly or 500 μg/week intranasally	Vitamin B12 ≥350 μg/day orally, replace with additional doses if deficiency confirmed

*Adapted from Mechanick JI, Kushner RF, Sugerman HJ, *et al*. American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic and Bariatric Surgery Medical Guidelines for Clinical Practice for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient. Perioperative bariatric guidelines. *Obesity* 2009;17:s1–s7050, with permission

WHAT TO EXPECT DURING AND AFTER A PREGNANCY

Several case reports and case series report serious complications of bariatric surgery during pregnancy, including intestinal obstruction, anastomotic leaks, band erosions or migration in LAGB and gastrointestinal hemorrhage[53–56]. One study reported that band migration may be more common in pregnancy, as its occurrence was 2.4% over the gestational period (approximately 40 weeks) vs. 6% over 10 years in non-pregnant patients[57]. Two maternal deaths during pregnancy have been reported[58,59]. Surgical complications may be difficult to diagnose during pregnancy as a result of the physiological changes that occur and a misplaced reluctance to perform appropriately indicated imaging studies during pregnancy. Clinicians should counsel their patients about common pregnancy complaints (nausea, vomiting, abdominal pain) which may signal a surgical complication and have a low threshold to intervene for a suspected surgical complication.

Dumping syndrome can occur after RYGB when refined sugars or high glycemic carbohydrates are ingested. Symptoms include abdominal cramping, nausea, vomiting and diarrhea. In addition, hypoglycemia can occur resulting in tachycardia, palpitations, anxiety

and diaphoresis. Unfortunately, screening for gestational diabetes with the 50 g glucola may precipitate this syndrome. As such, alternative methods to diabetes screening are recommended including home glucose monitoring with fasting and 2-hour postprandial blood sugars for 1 week during the 24–28 weeks of pregnancy.

Pregnancy has never been a time for weight loss, and no recommendations for caloric restriction during pregnancy have been forthcoming even if the patient is still overweight or obese. Close monitoring of maternal weight gains or losses is recommended with targeted weight gains as suggested by the Institute of Medicine[60]. If there is a concern regarding abnormal fetal growth, repeated ultrasound examinations should be used for evaluation.

Prior bariatric surgery should not affect the delivery timing, labor course, or delivery route. Nor is it an indication *per se* for a cesarean delivery. If a patient had complications from bariatric surgery that required surgical revision, then an intraoperative consultation with a bariatric surgeon is recommended in the event of a cesarean delivery.

Many patients remain obese after bariatric surgery. Furthermore, in reports of pregnancy after bariatric surgery, high rates (up to 80%) of obesity were reported[43,46,51]. As such, clinicians should also counsel patients who are still obese after bariatric surgery separately on the risks of obesity in pregnancy (often defined as a prepregnancy BMI >30 kg/m^2). Continued nutritional monitoring and supplementation is important in the postpartum bariatric surgery patient as several case reports describe nutritional deficiencies and failure to thrive in breastfed infants[61–64].

CONCLUSION AND FUTURE DIRECTIONS

Counseling the patient contemplating a pregnancy or currently pregnant after bariatric surgery is becoming common, but it is a complex issue with minimal evidence-based medicine available for guidance or support. Key issues include increased fertility after bariatric surgery and assessing nutritional status (folate, iron, vitamin D and B12 and calcium). Although it seems logical to conclude that perinatal outcomes would be improved with an optimal prepregnancy BMI, whether weight loss prior to pregnancy improves future perinatal outcomes has only been studied with respect to bariatric surgery patients. Indeed, the best choice of bariatric surgery procedure (restrictive vs. mixed) for a woman considering a pregnancy after bariatric surgery is not known. Given the present trends in obesity as well as the increasing numbers of bariatric surgery procedures, clinicians will be providing care for more bariatric surgery patients in the future. Knowledge of the procedures, outcomes and pregnancy after bariatric surgery is important to provide optimal care and counseling. As is often the case, however, as medicine approaches new frontiers, further studies are needed to determine the best management in pregnancy as well as short- and long-term maternal and infant outcomes.

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SECTION 7

Miscellaneous conditions

30

Obese nulliparas

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INTRODUCTION

Definition and epidemiology

Obesity is a condition in which body weight reaches a level high enough to endanger health. It is most commonly described in terms of body mass index (BMI) kg/m^2, which is the current gold standard measurement of adiposity. The classification into groups is shown in Table 1[1].

In addition to the BMI, a number of other methods are used increasingly in the non-pregnant adult to assess and describe obes ity. For example, waist circumference is widely considered a simple and accurate predictor for type 2 diabetes[2]. An increased waist-to-hip ratio has significant association with myocardial infarction[3] and the metabolic syndrome as well as subfertility[4] and development of gestational diabetes[5]. In contrast, bioimpedence (a measure of the opposition to the flow of electric current through tissues) is an ineffective measure of adiposity. Within obstetrics, the most widely used measurement is BMI.

Table 1 Classifying overweight and obesity[1]

Classification	*BMI*
Healthy weight	18.5–24.9
Overweight	25–29.9
Obese I	30–34.9
Obese II	35–39.9
Obese III	40 or more

The prevalence of overweight and obesity is rising throughout the developed, and to some degree, the developing world. The surgeon general of the United States describes it as a greater public health threat than smoking. In the UK, it represents one of the greatest (and growing) overall threats to the childbearing population[6]. Two-thirds of Americans are overweight and, of these, half are obese[6]; in the UK, 25% of adult women are obese[7,8]. In general the increase in obesity prevalence is a phenomenon of the past few decades, although one US study suggests that it now appears to be leveling off, at least in women[9]. Obesity appears to be at least superficially related to social class. Whereas in the mid-19th century the higher socioeconomic groups were at greatest risk, today it is the reverse[8], as lower socioeconomic populations consume an energy-dense and nutrient-poor diet[10]. That having been said, there is a general consensus that dietary content has changed greatly in the past 150 years with great reductions in the daily consumption of fruit, vegetables, breads and grain related products[11].

HOW DOES OBESITY AFFECT MOTHER AND FETUS?

Conception and miscarriage

Both fertility and maintenance of early pregnancy are affected by obesity. Although it is difficult to differentiate between the effects of obesity and polycystic ovarian syndrome and diabetes, obesity is independently associated with anovulation. This was clearly demonstrated in the large cohort US-based Nurses' Health Study II[12] and other smaller studies[13]. Insulin resistance is likely to be the main contributing factor. Ovarian physiology is altered both by directly increasing ovarian steroidogenesis and by reducing sex hormone-binding globulin synthesis, which leads to higher free androgen levels[14]. Another factor that has been identified as a possible causative agent is a elevated mullerian inhibiting substance, characteristically raised in polycystic ovarian syndrome, but also independently associated with anovulation in obesity[15].

Although anovulation is the main factor causing subfertility in obesity, there are others as well. A high BMI reduces the spontaneous pregnancy rate in both ovulatory women[16], and in women without menstrual irregularities[17] by an unknown mechanism.

Early miscarriage is four times more likely in obese women, although some evidence exists that women with a BMI of 25–30 have no increased risk[18]. Obesity is also a factor in recurrent miscarriages[19,20].

Evidence for the influence of obesity on *in vitro* fertilization outcome is abundant, but conflicting. An increased early miscarriage rate, and a resultant reduced live birth rate are both firmly established[21]. Several large studies show a higher cancellation rate (due to poor ovarian follicle response) with BMI >27[22,23]. Implantation rates and fertilization rates are not significantly reduced[21].

Antenatal complications

Hypertensive disorders of pregnancy

The linear association between weight and hypertension in pregnancy (both systolic and diastolic) is well established[24,25]. In fact, an increased BMI is a stronger risk factor for severe than for mild gestational hypertension[26]. The association between obesity and pre-eclampsia is also indisputable[27,28]. The risk of pre-eclampsia is doubled with a BMI of 26 and tripled with a BMI of 30 compared to a BMI of 21[28]. The same association is not present with the HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, supporting the hypothesis that the disease mechanisms are different[29]. The pathological processes are not fully understood; however, oxidative stress, inflammation and altered vascular function have been proposed[30]. Increased serum triglycerides are independently correlated with risk of pre-eclampsia[31]. As much as one-third of the effect of BMI on pre-eclampsia may be mediated through triglycerides and inflammation[32]; cholesterol levels may also be similarly correlated[25].

Gestational diabetes

Although the screening criteria for gestational diabetes mellitus (GDM) remain subject to controversy, the role of maternal weight as a risk factor is certain. The correlation between BMI and GDM is direct: a large meta-analysis calculated the odds ratios of developing GDM for overweight, obese and severely obese women as 2.1, 3.6 and 8.6, respectively[33]. Interestingly, however, once a diagnosis of GDM is made, pregnancy outcomes are similar regardless of maternal BMI[34]. Weight gain during pregnancy may also be a significant risk factor for diabetes, as mid-trimester BMI is more predictive than pre-pregnancy BMI[35].

Thromboembolism

Venous thromboembolism (VTE) is the leading cause of direct maternal death in the UK. The incidence in pregnancy is about 85 per 100,000 and two-thirds of these are postnatal. Obesity is a well documented risk factor for VTE. Both BMI >25 and delivery by cesarean section independently almost double the risk of postnatal VTE[36].

Labor and delivery

Obesity increases most risks for labor and delivery. As BMI increases, the chance of spontaneous onset of labor at term decreases[37,38]. When the BMI is >30 the chance of spontaneous labor declines by as much as 50%. Excessive weight gain between the first and third trimesters is also associated with longer gestation[37]. Although the risk of spontaneous preterm labor decreases with increasing BMI, the risk of having a premature baby is increased due to medical intervention[39], as induction of labor is increased, due in part to the increased numbers of postdate pregnancies[38,40], as well as the medical disorders mentioned above.

The association between pre-pregnancy maternal BMI and cesarean section risk is linear, and consistently observed in many cohort studies[37,41,42]. The odds ratio for cesarean delivery is 3.2 when BMI is >30 compared with normal[42]. Not only is BMI an independent factor for cesarean delivery, but it may also have a more significant impact than GDM[43]. Excessive weight gain during pregnancy also acts as a predictor of cesarean delivery independent of pre-pregnancy BMI and diabetic status[44]. The explanation for this increased risk is probably multifactorial, but failure to progress in labor caused by macrosomia and soft tissue dystocia (fat tissue accumulation narrowing the genital tract) has been proposed[45]. Obesity may also impair the ability of the uterus to contract in labor[46], contributing not only to the increased risk of cesarean delivery, but also to prolonged pregnancy duration. Difficulty performing and interpreting tests of fetal well-being such as ultrasonography, cardiotocography and fetal blood sampling may also be contributory.

Anesthetic complications

A number of important issues are related to the administration of anesthesia in the obese, the most important being difficulty of endotracheal intubation (15%) with increased rates of oxygen desaturation[47]. This latter problem is the result of BMI-exacerbated pregnancy-related reduced lung capacity and increased work of breathing. The already overloaded cardiovascular system is further stressed by the physiological changes of pregnancy. The very high demand for cardiac output can result in congestive cardiac failure[48] and the strong association between obesity and hypertension and diabetes increases the risk of ischemic heart disease. Gastro-esophageal reflux is a common problem in pregnancy and is exacerbated by the increased gastric volume and hiatus hernia so commonly found in obese patients[49]. Concomitant with these problems, aspiration under anesthesia is increased. The major alternative to general anesthesia, regional blockade, is technically more difficult due to problems in identifying the midline and epidural space, and subsequent dislodgement of catheters. This combination of factors can result in an initial failure rate of up to 42%[50].

Of the four deaths directly attributed to anesthesia in the UK 2007 CEMACH report[6], two women had BMIs >35; in each case death was caused by airway problems.

On the other side of the coin, some changes associated with pregnancy are actually beneficial to the obese woman. For example, the increased sensitivity of the respiratory center to carbon dioxide protects against obstructive sleep apnea, which is a risk in obese women[48].

Death

Obesity was highlighted as a risk factor for maternal mortality in both the 2004 and 2007 UK CEMACH reports[6,51]. Fifty-two per cent of deaths in the triennium ending 2005 were in overweight women (BMI >25). The most important causes of death amongst the obese are thromboembolism, sepsis and cardiac disease[6]. The same is likely to be true elsewhere in the developed world; however, in no other country is there such a comprehensive national audit on maternal mortality. In fact, only rarely do national-level databases containing information on pre-pregnancy weight even exist.

Postpartum

The adverse delivery and postpartum events associated with obesity such as operative vaginal and abdominal delivery, macrosomia and shoulder dystocia[38] all increase the risk of postpartum hemorrhage. Postpartum anemia is increased independent of hemorrhage[52].

Infectious morbidity is increased from postcesarean wound infections, endomyometritis and urinary tract infections. This relationship remains true for both elective and emergency operations, even when prophylactic antibiotics are administered[53,54].

As pre-pregnancy BMI increases, successful breastfeeding duration shortens. Whether social context is the whole or part of the explanation for this finding is not clear; nor is it clear if this phenomenon is universal or restricted to the Danish study population[55].

Fetus

Birth defects

The association between obesity and fetal neural tube defects (NTDs) is well established. Compared to normal-weight women, offspring of mothers with a BMI of >30 have approximately twice the chance of being affected[56]. Although maternal diabetes is also a risk factor, obesity remains significant after adjustment for this[57]. In addition to NTDs, cardiac malformations more recently were shown to be increased for both the overweight and obese[58]. The association is strongest with atrial and ventricular septal defects[59].

Several mechanisms have been proposed for these associations, though none are confirmed. As hyperinsulinemia is a known independent risk factor for NTDs, one explanation is that many obese women have undiagnosed glucose intolerance. Poor quality diets resulting in nutritional deficits may also be causative.

Macrosomia and shoulder dystocia

It is axiomatic that obese women deliver large babies[40,45,60]. In this regard, maternal BMI exerts an even stronger influence than GDM on this risk[43]. The influence of excess weight gain during pregnancy (defined as 7–11 kg for women with BMI >26) on this risk is interesting. Neither overweight women with normal weight gain, nor normal-weight women with excess weight gain are at risk; risk only accrues to overweight women who gain excess weight. Accordingly, an overweight woman can reduce her chances of delivering a large baby by moderating her weight gain during pregnancy[61].

Shoulder dystocia is an essentially unpredictable event; however, its incidence rises incrementally with increasing birth weight. When GDM is present, the incidence is further increased[62]. This having been said, maternal BMI has not been shown conclusively to be an independent risk factor as evidence on this point is conflicting[38,63,64].

Assessment of fetal well-being

All methods of determining fetal well-being are notoriously difficult in the obese woman.

Excess abdominal adiposity complicates measurement of fundal height, ultrasound visualization of the fetus and cardiotocography (CTG). Fetal blood sampling is also physically more demanding when the woman is heavy. Inevitably, this could lead to failure to recognize fetal compromise with subsequent poor outcome. Despite widespread acceptance of this hypothesis, it has been difficult to prove in clinical trials. Indeed, accuracy of sonographic fetal weight estimation was unaffected by BMI in two studies[65,66]. Regardless, visualization of the cardiac and craniospinal structures is suboptimal[67], and fetal blood sampling takes longer as BMI increases[68].

Stillbirth

The association between increased BMI and stillbirth has been established by meta-analysis showing an incrementally increased risk with increasing BMI[69]. Obese women have double the risk of stillbirth (odds ratio of 2.1)[70]. No single cause of death can explain this risk; however, there are more 'unexplained intrauterine deaths', and fetoplacental dysfunction is more common[71].

Infant

Offspring of obese women are at risk of childhood obesity that continues on into adolescence and perhaps later in life[72,73]. The association is strongest, however, for macrosomic babies[73,74], and there is a strong link between maternal obesity and macrosomia which is not dependent on maternal diabetes mellitus. Perhaps even more concerning is the two-fold increased risk of developing childhood metabolic syndrome (obesity, hypertension, dyslipidemia and glucose intolerance) in infants born to obese women, and those born macrosomic (regardless of maternal diabetic status)[75].

WHAT SHOULD BE DONE TO OPTIMIZE MATERNAL AND FETAL OUTCOME?

Weight loss

How much?

For women seeking fertility treatment, the UK National Institute for Health and Clinical Excellence (NICE) states that a BMI of <30 should be achieved before commencing assisted reproduction, as a BMI >30 is likely to reduce the success of all procedures[76]. In the case of obese anovulatory women, weight loss assists with resumption of ovulation and improves pregnancy rates[77–79]. However, the British Fertility Society recommends that 'Women with a body mass index of <19 and >29 should be referred for advice from a dietician, warned of the risks in pregnancy, if appropriate, and provided with access to exercise advice and offered psychosocial support. NHS funding of their infertility treatment should be deferred until they demonstrate response to these interventions. If the menstrual cycle is regular and the FSH normal, assisted conception may be provided if the BMI is <36.'[80]. As funding for infertility treatment is actually dependent on geographical location within the UK, differing upper BMI limits apply. As assisted conception is funded privately elsewhere in the developed world, other countries do not define strict inclusion criteria. However, the Canadian Fertility and Andrology Society advises a supervized weight loss program if BMI is >30 before referral to infertility services. Preconceptional weight loss is not only practically difficult, but the stipulation to lose weight before attempting assisted conception can exacerbate already significant psychological morbidity.

Barker's hypothesis of 'developmental origins of adult health and disease' states that environmental factors, particularly maternal undernutrition, act in early life to program risks for later life adverse health outcomes[81]. It is postulated that the pituitary–adrenal axis may

be reprogrammed to produce excess glucocorticoids, thus resulting in pathologies such as cardiovascular disease and the metabolic syndrome in adult life. It has been hypothesized that dieting pregnant women may also be at risk of this outcome, though never proven. However, exposure to *in utero* overnutrition, i.e. maternal hyperglycemia can result in poor health outcomes, such as obesity, that emerge in childhood and adolescence[82]. Therefore, it would seem prudent to maintain a balanced diet throughout the preconceptional and early gestational periods with weight loss occurring at a steady pace. The recommended maximum weekly weight loss for obese adults is 0.5–1 kg with the target of losing 5–10% of the original weight. The change from losing weight to maintenance should occur after 6–9 months[1]. These recommendations have not been studied specifically in the preconceptional period. It may be sensible to prescribe vitamin and mineral supplements containing the reference quantities if significant weight loss is occurring.

Once pregnancy has begun, the recommended weight gained is dependent on a woman's pre-pregnancy BMI. The Institute of Medicine in 1990 produced a report titled 'Nutrition during pregnancy' which advises that weight gain for pregnancies should be inversely correlated to pre-pregnancy BMI (Table 2)[83,90]: these figures have since been ratified by prospective data[84]. In terms of obese women, weight gain of less than 7 kg has no negative impact on pregnancy or neonatal outcome[85]. On the contrary, a recent Missouri population-based cohort study described reduced risks of pre-eclampsia, cesarean section and macrosomia in obese women who lost less than the recommended 7 kg during pregnancy[86]. We also know that gaining more than 7 kg during pregnancy results in a two- to three-fold further increase in weight retention postpartum[87]. This is particularly significant for the nulliparous woman who, with each successive pregnancy, will have increasing pre-pregnancy BMI with its associated increased risks.

Table 2 Recommended total weight gain ranges for pregnant women with singletons by pre-pregnancy BMI[90]

BMI	*Recommended weight gain* (kg)
Low (BMI <19.8)	12.5–18
Normal (BMI 19.8–26.0)	11.5–16
High (BMI >26.0–29.0)	7–11.5
Very high (BMI >29)	>6.8

Strategies

The UK national guideline on management of obesity in non-pregnant adults offers a template for deciding the initial level of intervention required according to the woman's BMI and waist circumference (Table 3)[1]. The US National Institutes of Health's guideline on the treatment of overweight and obesity in adults advises the use of pharmacological strategies in patients with a BMI >30 or >27 with concomitant risk factors, and surgery for patients with a BMI >40 or >35 with comorbid conditions and acceptable operative risks[88]. Applying this to the preconceptional situation is considered below.

Conservative

Within the context of a preconceptional counseling session, physicians should ensure that an extended consultation is booked so that the many risks outlined above can be discussed, the extent of detail being tailored to the patient's understanding. In some instances, the presentation of this information alone can initiate motivation to lose weight. However, due to lack of time, resources and knowledge[89], clinicians often are poor counselors, so much so that obesity management training for the

Table 3 A guide to determining the initial level of intervention to consider[1]

	Waist circumference			
BMI	*<80 cm*	*80–88 cm*	*>88 cm*	*Comorbidities present*
25–29.9	Advice	Conservative	Conservative	Medical
30–34.9	Conservative	Conservative	Conservative	Medical
35–39.9	Medical	Medical	Medical	?Surgical
40 or more	?Surgical	?Surgical	?Surgical	?Surgical

clinician may be warranted[90]. Other than informing the woman of the risks, the consultation should include a discussion about why they have gained weight as well as their diet and activity levels. Admittedly, individuals from various ethnic and socioeconomic backgrounds may be at greater risk from obesity and may have different attitudes and beliefs about weight management. Weight loss strategies previously used should be reviewed and an assessment of the patient's readiness to change should be made[1].

Group weight loss programs involving both exercise and dietary advice have a far greater impact on weight loss compared to the standard clinical approach[91–93]. This is particularly true for obese infertile women who are more likely to conceive and less likely to miscarry if they are participating in a group program than operating as an individual[94]. Accordingly, information about local patient support programs should be readily available.

Exercise should be encouraged for both weight loss and other health benefits; targets should be realistic. Activities that can be incorporated into everyday life will be better adhered to. The UK recommended level of activity for overweight adults is 30 minutes of moderate-intensity activity, e.g. brisk walking or cycling on five or more days a week. This level of activity is also perfectly safe in pregnancy, so any fears that this could harm an early pregnancy can be dispelled[95].

Medical

Currently, two commonly used pharmacological interventions facilitate weight loss: appetite suppressants (sibutramine, rimonabant); and lipase inhibitors (orlistat). Medical treatment should always be used in combination with the conservative measures outlined above. All medical treatments are contraindicated in pregnancy but data are scant; therefore contraception is imperative during therapy. Meta-analyses assessing the efficacy and safety of these drugs have shown them all to be superior to placebo, but weight loss is only moderate (less than 5 kg more than placebo), and drop-out rates are very high. Moreover, no long-term data are available on their eventual effect on cardiovascular morbidity[96,97], though this health benefit may be more significant than the weight loss itself to the preconceptional woman, as its impact on her future fertility, pregnancies or offspring is doubtful.

The choice of drug can be steered by the patient's preference, local drug costs and the patient's comorbidities. Rimonabant is the most effective for weight loss, improves blood pressure and triglyceride levels, and increases high density lipoprotein levels. However, psychiatric disorders are increased and rimonabant should be avoided in women with any psychiatric history. Sibutramine also improves triglyceride levels and increases high density lipoprotein concentrations; however,

blood pressure and pulse are increased. Pre-existing cardiovascular disease, uncontrolled hypertension and tachycardia are therefore contraindications. Orlistat is the least effective for weight loss, but the secondary benefits are significant, including a reduced incidence of type II diabetes (shown in one 4 year trial)[98], and reductions in blood pressure, fasting glucose and hemoglobin A_{1C} concentrations in patients with diabetes, as well as total cholesterol and low density lipoprotein concentrations. There is, however, a 15–30% rate of gastrointestinal adverse effects, and due to its malabsorptive mechanisms, patients are usually advised to take mulitvitamins on a daily basis, even though clinically relevant vitamin deficiency has not been reported[96].

Surgical

Obesity surgery is an option for the obese who have failed conservative and medical treatment. Postoperative weight loss is far in excess of that which medical or conservative therapy can offer. A mean loss of over 60% can be expected for the morbidly obese with resolution of comorbidities including diabetes, hyperlipidemia, hypertension and obstructive sleep apnea in the majority of patients[99]. The American College of Obstetrics and Gynecology (ACOG) recognizes bariatric surgery as suitable treatment in the preconceptional woman[100]. Neither the Royal College of Obstetricians and Gynaecologists (RCOG) nor the Society of Obstetricians and Gynaecologists of Canada (SOGC) have made statements regarding surgery for the preconceptional woman.

Procedures are either restrictive (gastric banding) (commonest in the UK), malabsorptive (gastric bypass) or hybrid (biliopancreatic diversion). The description of these operations is beyond the scope of this chapter, although, it is worthwhile understanding the mechanisms and common complications so that patients can be informed. Restrictive procedures work by limiting the amount of solid food that can be ingested at any one time. The patient should chew well and eat slowly, or vomiting can result. Weight loss is achieved mainly through an unpleasant sense of fullness. Malabsorptive procedures cause the stomach to have very limited digestive capacity, exposing the lower gut to undigested nutrients. This gives rise to satiating signals, and diarrhea is a common side-effect.

The conventional indication for surgery has been a BMI >40 or BMI >35 with comorbidities. Increasingly, studies are looking at operating on women with a BMI of 30–35[101,102] owing perhaps to the impressive results and improving safety profile accompanying laparoscopic operations. UK guidelines recommend that a candidate should have tried all appropriate non-surgical measures for at least 6 months, be generally fit for anesthesia and surgery, and be committed to long-term follow-up[1].

The risk of fetal undernutrition is the greatest concern for preconceptional women contemplating surgery. Nutrient complications are much less likely with restrictive than with malabsorptive procedures, and can be prevented with monitoring, dietary advice and supplementation. Macronutrient deficiencies include protein-calorie malnutrition and fat malabsorption; and the commonest micronutrient deficits are iron, calcium, folate and vitamin B12[103].

After bariatric surgery the benefits of weight loss on pregnancy are great and certainly seem to outweigh any potential adverse effects. Conception rates improve, though the miscarriage rate has not been shown to decrease[104]. Early concerns about increased rates of preterm birth and intrauterine growth restriction have not been verified with larger studies. In fact, not only is there good evidence showing that perinatal outcome is not adversely affected[105–107], but pregnancy complications such as hypertensive disorders, gestational diabetes and macrosomia are also significantly reduced compared to non-surgically treated obese women[104,108,109].

The adjustability of gastric bands (enabled via a small access port positioned under the skin) makes them an attractive option for preconceptional women, as it allows modification of the sphincter size as the requirements change through the pregnancy. During the first trimester, for example, it can be loosened if hyperemesis is a feature. A group in Australia have shown that 'active management' of the band in pregnancy has enabled many women to achieve the Institute of Medicine (IOM) recommended weight gain[106]. However, there are not as yet established guidelines on the management of a gastric band in pregnancy.

ACOG has made recommendations concerning women who have undergone bariatric surgery before commencing pregnancy[100]. Women should be advised that they are at risk of becoming pregnant unexpectedly following surgery and should delay pregnancy for 12–18 months to avoid conceiving during the rapid weight loss phase. Theoretically, this will promote optimal maternal condition as well as avoid potential nutritional deficiencies; however, evidence supporting this admonition is minimal and inconclusive[104,107,110].

General measures

Inherent in any preconceptional weight reduction program is the need for good contraception so that the target weight can be achieved before pregnancy begins; the obvious choice is a barrier method. The reasons for this include the elevated thromboembolic risk with the combined oral contraceptive, the delay in return of fertility with depot injectables, the reduced efficacy with progesterone only pills (POP) and risk of pelvic inflammatory disease with intrauterine devices. In addition, the progesterone implant can be considered, as failures attributable to BMI have not occurred, and the desogestrel POP which acts to inhibit ovulation is likely to be unaffected by BMI[111].

It is imperative that obese women are strongly advised to take folic acid supplementation as they are not only at a heightened risk of fetal neural tube defects, but have also been shown to be less reliable medicators[112]. The question of high dose supplementation of the obese has not been answered, but the RCOG recommendation is to 'consider high-dose folic acid (5 mg/day)' in severely obese women (BMI >35) (consensus views 53rd study group). Some evidence supports this. For example, one study showed that the usual dose of 400 μg had no protective effect for women weighing over 70 kg[113]. In addition, a Canadian study demonstrated that flour fortification only benefited lighter women and not the heavier, by calculating odds ratios for the risk of maternal obesity on NTDs before and after flour fortification was introduced (OR 1.4 versus 2.8). This could mean that obese women require higher doses, but could also mean that the increased risk of NTDs is independent of folate intake[114].

Vitamin D deficiency can occur during periods of high demand including intrauterine life, infancy, childhood and pregnancy. As 90% of vitamin D is synthesized in the skin by exposure to sunlight, considerable variations occur secondary to geographical latitude and skin color. It is well documented that obese individuals have lower vitamin D levels[115,116], the mechanisms for this being partly vitamin D's accumulation in fat cells and possibly a reduced production. Because there is a direct correlation between maternal and neonatal vitamin D deficiency[117] it follows that increased vitamin D levels in the pregnant woman will benefit the child. In addition, improved vitamin D status in the mother reduces the risk of childhood osteoporotic fracture and wheeze[118,119]. NICE now recommends vitamin D supplementation of 10 μg/day to all pregnant women with a BMI >30[120]. It would be worthwhile and without risk to start vitamin D in the pre-pregnancy period so that levels can accumulate.

CONCLUSION

The management of obesity has long been poorly understood and, as a consequence, the condition has been largely ignored. The subject can be difficult to broach and requires sensitivity on the part of the clinician, but its significance must not be underestimated. Active management can reap great benefits to the patient, and even greater benefits to the preconceptional patient.

The main obstacle to achieving good preconceptional care of obese women is logistical. These women do not present to the medical profession unless there are comorbidities or fertility problems. However, these opportunities should not be missed, and systems need to be put into place in medical and fertility clinics to ensure preconceptional counseling can take place. The ACOG Committee Opinion on preconception care recommends 'screening of all reproductively capable women on an ongoing basis to identify potential maternal and fetal risks to pregnancy'[121]. Medical practitioners should take opportunities wherever possible to ask women about their intentions for pregnancy so that counseling can be arranged in good time.

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31

Counseling in couples with genetic abnormalities

Tessa Homfray

INTRODUCTION

For the past several decades, women have been having their babies later in life. As a result, many are developing diseases that are not as common in younger women. Unfortunately, these diseases often affect the outcome of pregnancy. At the same time, other women have diseases which were previously incompatible with long-term survival and now, after therapy, these women wish to have their own families. These two previously unknown circumstances, plus an increasing awareness of genetic disorders, are leading more and more potential parents to seek specialist genetic advice on pregnancy planning, investigations and management prior to conception. Such information is available in all regions of the UK as well as in other developed and in some developing nations. In the case of the UK, the addresses from which to obtain local services can be found on the British Society for Human Genetics website[1] and the American Society of Human Genetics[2].

The family history is, and for the foreseeable future will remain, the basis of genetic counseling. Medical personnel involved with patients during antenatal care should be able to take and document a simple pedigree, and know when referral for specialist advice is required (Figure 1).

A number of pregnancies can be recognized to be at increased risk of fetal abnormalities and/or a genetic syndrome prior to the pregnancy. As such, they are suitable for preconceptional counseling and special attention and management.

Factors indicating that preconceptional counseling should be considered and discussed in this chapter include:

- Advanced maternal age
- Advanced paternal age
- Risk of fetal exposure to teratogens
- Consanguinity
- Known genetic syndrome within the family
- Unexplained physical or mental handicap within the family
- Genetic causes of infertility
- Maternal disease.

An increase in maternal age is the internationally recognized factor for Down's syndrome and is often understood by the patient; however, this knowledge is commonly thought to be limited to Down's syndrome and other risk factors are less well recognized and may need to be proactively asked about by the health professional. Families have frequently believed that birth injury had been the cause of abnormalities, and it is always necessary to untangle fact from fiction in family stories. The above risk factors are discussed in more detail below.

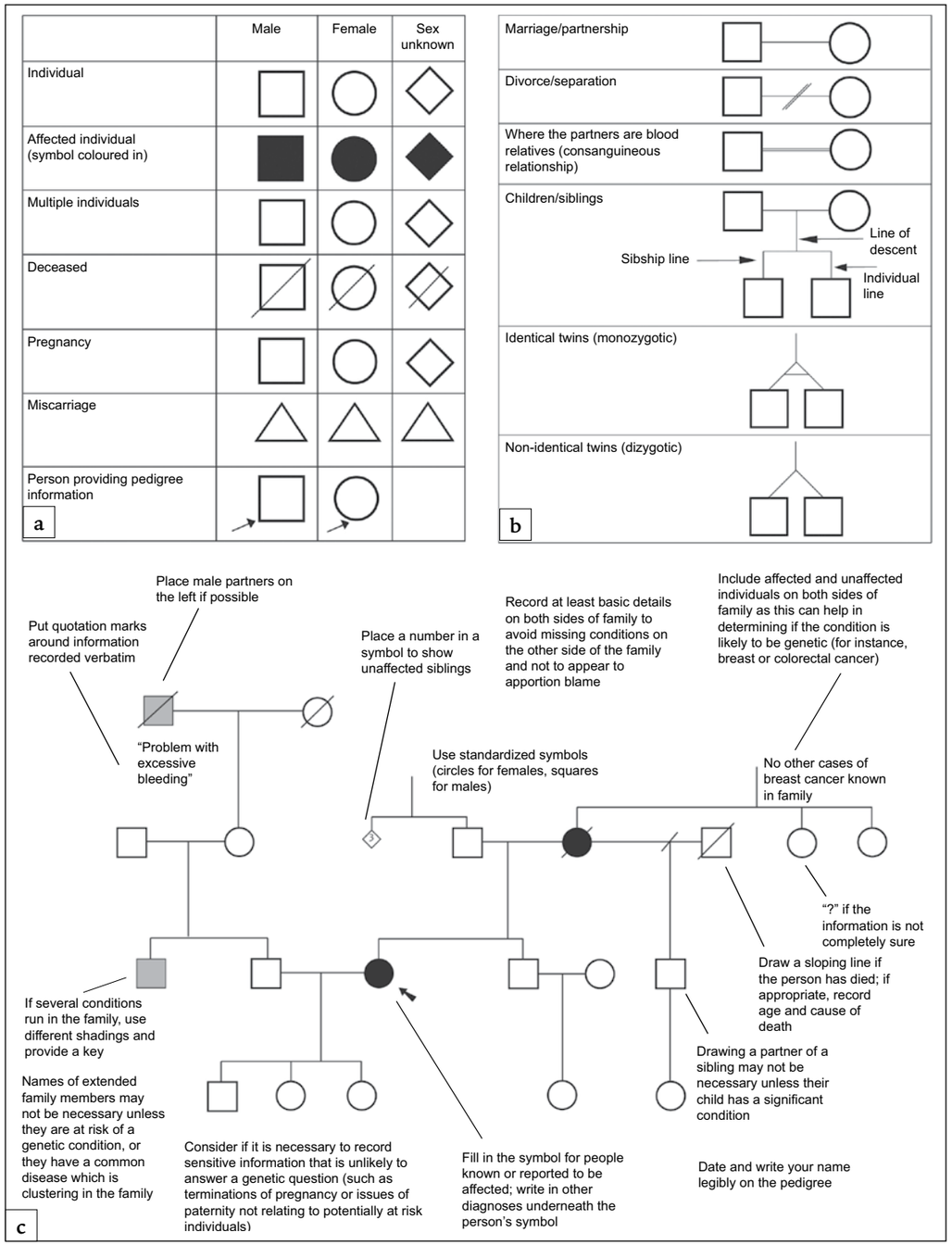

Figure 1 Pedigree. (a) Examples of most commonly used pedigree symbols. (b) Examples of relationship lines. (c) Example of a pedigree. Reproduced from National Genetics Education and Development Centre (www.geneticseducation.nhs.uk)[3], with permission

ADVANCED MATERNAL AGE

Advanced maternal age leads to an increased risk of pregnancies with a trisomic karyotype. Down's (trisomy 21), Edward's (trisomy 18) and Patau's (trisomy 13) syndromes are all well recognized, and screening programs are available for early-stage identification in pregnancy. Other chromosomal trisomies also may occur and lead to early miscarriage or occasionally trisomic rescue. In trisomic rescue, the fetus has 47 chromosomes at conception but loses a chromosome early on in gestation, so that the remaining number is 46. The chromosome lost during this process may be from the parent who passed on only a single copy, so that the baby will have inherited two copies from the other parent. If trisomic rescue affects an imprinted chromosome (6, 7, 11, 14, 15 and possibly 20), this process may lead to major fetal abnormality. (Imprinting is the phenomenon whereby a small subset of all the genes in the genome is expressed according to their parent of origin.) Screening programs do not pick up all cases of the major trisomies, and it is important that couples are aware of the difference between screening and diagnostic tests. Moreover, screening programs vary across the world, and only in a few countries is there a coordinated transparent approach to screening. Technological advances, especially with the arrival of free fetal DNA technology, may change this over the next few years.

ADVANCED PATERNAL AGE

Increasing paternal age results in primary spermatogonia originating from germ cells which have undergone an increasing number of mitoses, which in turn give rise to an increased chance of gene mutations. As a result, single gene disorders arising as new mutations are commoner in progeny of older men. Examples of this process include achondroplasia and Apert's syndrome. Point mutations in the dystrophin gene more commonly arise in spermatogenesis than in oogenesis, whereas partial gene deletions more commonly arise in oogenesis. Under these circumstances it is possible to see that if there is a single case of Duchenne muscular dystrophy within the family, the type of mutation may dictate the likely origin of the mutation.

EXPOSURE OF THE FETUS TO TERATOGENS

Recreational and therapeutic drugs, and intrinsic maternal metabolites can cause teratogenic effects in the fetus.

Recreational drugs

Alcohol in the first trimester of pregnancy can lead to a number of morphological abnormalities in the fetus such as partial agenesis of the corpus callosum and subtle facial dysmorphic features. Prolonged exposure leads to intrauterine growth retardation and poor brain growth, which may result in learning difficulties and attention deficit hyperactivity disorder. The disorder is commonly characterized as the fetal alcohol syndrome and has been described in detail for the last several decades.

Cocaine abuse is a far more recent phenomenon. It causes major brain abnormalities with septo-optic dysplasia and schizencephaly among those implicated. Cerebral infarction in the newborn has also been reported. Other vasoactive drugs such as amphetamines may cause similar effects. These effects are in contrast to *in utero* exposure to opiates which causes withdrawal symptoms in the neonate but no structural abnormalities.

Smoking, which is not always thought of as recreational drug, causes intrauterine growth retardation and an increased risk of premature delivery and miscarriage.

Therapeutic drugs

Most drugs are contraindicated in pregnancy, as it is generally not possible to carry out clinical trials in pregnant women (only drugs for pregnancy associated diseases such as pre-eclampsia are actively studied in pregnancy). Despite this, many drugs have been used widely in pregnancy and appear to be safe. Certain drugs, however, are required for use in pregnancy for the treatment of maternal disease. Below are some with known associated syndromes; however, it is beyond the scope of this chapter to discuss fetal teratogens in depth, and all drug treatment in pregnancy should be carefully evaluated. It has become increasingly clear that there is an interaction between the fetal and maternal metabolism that determines the variable effects of therapeutic drugs on the fetus.

Anticonvulsants

Anticonvulsants are the most frequent and most well characterized teratogens to cause fetal abnormality in the developed world. Sodium valproate can cause spina bifida, congenital heart disease, dysmorphic features and learning difficulties[4,5]. If possible young women should be changed to a more suitable anticonvulsant prior to pregnancy. Lamotrigine and carbamazepine are the drugs of choice, although no anticonvulsants are completely safe and fetal abnormalities with carbamazepine have been recognized. Lamotrigine is a newer drug, and all the potential effects may not yet have been recognized. Any woman taking anticonvulsants should take 5 mg folic acid daily periconceptionally to try to reduce the effects of the fetal anticonvulsant syndrome. Once a woman has had one child with the fetal anticonvulsant syndrome, the chance of a further future child being affected is approximately 50%, whereas the overall risk for a first pregnancy is approximately 5%. The dose of folic acid for such women is also 5 mg daily.

Retinoic acid analogues

Retinoic acid analogues are well known teratogens used in the treatment of acne and psoriasis. Advice on the avoidance of pregnancy during treatment must always be provided, and the pharmaceutical community is well aware of this hazard and assists in cautioning women in the childbearing years.

Carbimazole

Carbimazole[6,7] is a common treatment for hyperthyroidism and is now recognized as causing a specific malformation syndrome.

Angiotensin converting enzyme inhibitors

Angiotensin converting enzyme (ACE) inhibitors[8] are used in the management of hypertension and cardiac failure. Diabetics are often treated for hypertension at a lower blood pressure than other patients owing to their increased risk of microvascular disease, and these patients are already determined to be at high obstetric risk.

Warfarin

Warfarin embryopathy results from its effect on vitamin K metabolism[9,10]. Patients with prosthetic heart valves and those with previous deep vein thrombosis or pulmonary embolus are those most likely to be taking warfarin. As the effects are mild, it would seem reasonable to change patients to heparin as soon as a pregnancy is confirmed for the remainder of the first trimester rather than preconceptionally in view of the inconvenience of heparin therapy and prolonged use potentially causing osteoporosis.

Most drugs are contraindicated in pregnancy in view of the potentially catastrophic effects that can be caused. A prime example is thalidomide, developed in the 1950s as a sedative and antiemetic, which caused major limb and other abnormalities. Since that time companies have been extremely reticent to market drugs approved for pregnant women. Many drugs appear to be safe, however, such as the serotonin uptake antagonists, beta-blockers after the first trimester unless they are being used for treatment of hypertension, beta-agonists, steroids and antibiotics. Regardless, tetracyclines should be avoided as they cause discoloration of the developing teeth. (For intrinsic maternal metabolites see section below on Maternal disease.)

CONSANGUINITY

Although marrying within the family is common in certain parts of the world, consanguinity occurs outside these communities as well. In the absence of any known abnormalities in the family, first cousin marriages have a 2–3% higher than background risk of having a child with an autosomal recessive disorder secondary to a rare recessive gene. If there is a known genetic disease within the family, this risk can increase dramatically. If the disorder has been characterized, however, it may be possible to test the carrier status of the at risk couple. In such instances, full diagnostic details must be identified in the affected patient, and referral to a geneticist is strongly recommended. It is mandatory to take a full family history including the common ancestor(s) of the couple. This is easier said than done, unfortunately, as the disease within the family may be extremely rare and the diagnosis may not have been confirmed among many of the affected relatives who may live abroad[11].

KNOWN GENETIC SYNDROME IN THE FAMILY

If a couple present with a known genetic syndrome within the family, it is important to obtain documentary evidence. A full family history should be taken including the dates of birth, addresses and hospitals where affected individuals were treated. Consent for release of information regarding the affected person may need to be obtained before further details can be accessed. Referral to a genetic center is recommended, as these centers are used to collecting relevant information. It is then necessary to ascertain whether a couple is at risk of having an affected baby and what they would wish to do if the baby were to be affected. If molecular or karotypic evidence is available, then the at risk member of the couple can be tested if necessary[3] (Figure 2). A number of considerations influence deciding whether a couple is at risk. The first of these is to determine the mode of inheritance of the disorder.

Autosomal dominant inheritance

Autosomal dominant inheritance is direct inheritance from one generation to the next. Even when present, it is important to recognize that the disease may vary between generations and affected children. If the disease does not present until later in life after the couple have reproduced, there will be no selection against the disease. Some diseases may show anticipation; this is the process by which a mutation changes as it passes from one generation to the next, and thus the disease may become more severe in successive generations. The severity may vary according to the sex of the carrier parent; examples include myotonic dystrophy and Huntington's chorea. If the mother is affected, then her health may be adversely affected for a pregnancy.

If inheritance is autosomal dominant, the following questions should be considered:

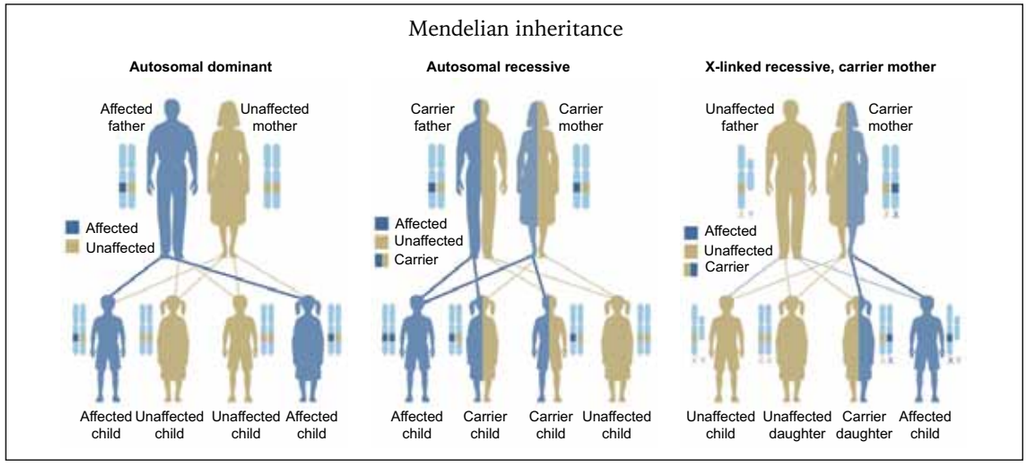

Figure 2 Inheritance patterns. Reproduced from US National Library of Medicine. (http://ghr.nlm.nih.gov/handbook/inheritance/inheritancepatterns), with permission

- Could the patient be mildly affected?
- Is the patient affected?
- Could the patient be an unaffected carrier?

Autosomal recessive inheritance

In autosomal recessive inheritance, both parents are carriers of a mutation, but the disease only manifests itself if a child inherits both copies of the abnormal gene. Hence, if the parents are well but carriers, every child has a 1:4 chance of being affected. The incidence of the disease depends on the carrier frequency within the population, and this often varies between ethnic groups. For example, the carrier frequency for sickle cell anemia is 1:8 in West Africans and 1:24 for cystic fibrosis in northern Europeans, whereas cystic fibrosis is almost unheard of in the Chinese.

Consanguineous couples show a higher incidence of autosomal recessive diseases in their offspring because they are more likely to share the same rare deleterious mutations, and they may have children with very rare and previously unrecognized diseases. If a parent is affected with an autosomal recessive disease it may be possible to test her/his partner to determine whether he/she is a carrier and whether future children would be at risk.

If inheritance is autosomal recessive, the following questions should be considered:

- Can the patient be tested for carrier status?
- Is the disease common enough so that the partner could also be a carrier?
- Is it possible to test a partner? In many diseases, a few common mutations cause the disease and these can be tested for, whereas in others there are no common mutations, and it is impractical to test an unrelated spouse for carrier status.
- Are the couple consanguineous and therefore could they share rare deleterious genes?
- Do the couple already have an affected child?

X linked

Women have two X chromosomes and men have only one. There are a few similar genes

on the Y chromosome in the pseudoautosomal region where the X and Y chromosome can pair at meiosis. As men are monosomic for most genes on the X chromosome, if there is a mutation on a gene located on the X chromosome, in nearly all cases males will be much more seriously affected. Duchenne muscular dystrophy is the commonest recognized X-linked disease with an incidence in boys of 1:3000.

In females partial expression may occur in some X-linked diseases, and this is frequently dependent on X-inactivation patterns; for example, Coffin-Lowry syndrome and fragile X syndrome. (X inactivation occurs in all people with more than one whole X chromosome. Only one X chromosome remains active, and the X chromsosome is inactivated as a random event. Therefore, in a women with two X chromosomes there should be an approximate 50:50 ratio for inactivation. If the inactivation is unequal and a high proportion of the X chromosome with the mutated gene remains active, a woman may be partially affected.) Some deleterious mutations may be lethal in early pregnancy in the hemizygous male, and only females are seen with the disease. Examples of the latter process include incontinentia pigmenti and Rett syndrome.

If inheritance is X-linked recessive, the following questions should be considered:

- Is molecular diagnosis possible?
- If molecular diagnosis is not possible as the affected patient died prior to molecular testing, can the carrier status be inferred using other family samples?

Non-Mendelian inheritance

Mitochondrial inheritance

Mitochondria have their own genome. All mitochondria are inherited from the mother. Therefore, if there is a mutation in the mother's mitochondrial genome all her offspring are at risk, but as each cell contains multiple copies of the mitochondrial genome, only some of which might contain the deleterious mutation, the number of abnormal copies inherited determines how severely/mildly the baby will be affected. This is known as heteroplasmy.

Epigenetic factors

Because epigenetic change in gene expression is not related to an underlying change in DNA sequence, it is therefore not passed on to future generations. An example is the imprinting defects causing Beckwith-Weidemann syndrome, although the genetics of Beckwith-Weidemann are complicated, and expert advice should be sought for recurrence risks in future pregnancies. Diseases with a parent of origin effect occur normally due to epigenetic changes such as methylation.

Free fetal DNA

Free fetal DNA (ffDNA) testing has only recently been introduced into clinical practice, and many patients will be unaware of its availability. If the patient is a carrier of an X-linked recessive disorder, preconceptional counseling should discuss fetal sexing using ffDNA. Blood for ffDNA testing can be taken from 8 weeks' gestation onwards[12]. Invasive testing will then only be required for male pregnancies. Congenital adrenal hyperplasia is an autosomal recessive disorder most commonly owing to a mutation in the 21 hydroxylase gene. An affected female fetus is at a 75% risk of developing moderate to severe clitoromegaly. Maternal dexamethasone treatment from approximately 7 weeks of gestation can be used for prevention. Only 1:8 at risk pregnancies will require this treatment and, by offering sexing by ffDNA, only women carrying female fetuses will need to continue the

steroids until chorionic villus sampling (CVS) can be performed at 11 weeks to determine whether the baby is affected. The applications for ffDNA are likely to expand widely over the next few years.

UNEXPLAINED PHYSICAL OR MENTAL HANDICAP WITHIN THE FAMILY

Many families have a family member with unexplained mental or physical handicap. A careful family history may suggest an X-linked disorder. Female carriers may be asymptomatic or may have mild disease manifestations. An X-linked history is suggested if there are two or more boys affected in two successive generations connected through unaffected or mildly affected females. To date, 60 genes have been identified to cause X-linked mental handicap resulting in syndromic (associated with other features than just mental handicap) and non-syndromic mental handicap[13]. Identification of X-linked inheritance is often difficult if only a single male or two male siblings are affected. In the latter case it is more likely to be as a result of an autosomal recessive gene rather than an X-linked gene. Another cause of unexplained physical or mental handicap, that could cause recurrence in a healthy couple without an affected child in the absence of consanguinity, is a syndrome with autosomal dominant inheritance with variable penetrance and chromosome translocations. In the past many parents believed that a baby was damaged at birth and, without good evidence of prematurity or cerebral palsy, this diagnosis should be viewed with caution. Chromosome analysis of the parent with the family history is a straight forward investigation which will exclude chromosome translocations except for cryptic translocations. A cryptic translocation cannot be identified by conventional cytogenetics; to date, this can only be diagnosed using fluorescent *in situ* hybridization.

Chromosome translocations

A chromosome translocation is the process by which two non-homologous chromosomes exchange chromosomal material between them and therefore do not have an identical pair to undergo crossing over at meiosis. There are two major forms of chromosome translocations.

Robertsonian translocation

Acrocentric chromosomes (13, 14, 15, 21 and 22) do not have short arms (p arms) that contain essential genes, and therefore two acrocentric chromosomes can join together with no deleterious effect on the carrier. The carrier will only have 45 chromosomes rather than the normal 46. This can lead to unbalanced chromosome rearrangements in the offspring of the carriers. The risk depends on the chromosome involved and the parent of origin of the translocation. The commonest Robertsonian translocation is 13:14 with an overall incidence of 1:1300[14,15]. Only trisomy 13 and 21 are viable; very rarely a trisomy 22 fetus can survive pregnancy.

Survival for trisomy 14 and 15 is only possible if the embryo undergoes trisomic rescue but, as both these chromosomes are imprinted, major fetal abnormalities will be present depending on the parent of origin of the chromosome (Figure 3).

Reciprocal translocation

Reciprocal translocation is an exchange of chromosomal material between two non-homologous chromosomes resulting in the same total number of chromosomes. These translocations are individually very rare, and it is often difficult to predict the likelihood of a fetus having an unbalanced karyotype as the result. The larger the translocated segment the

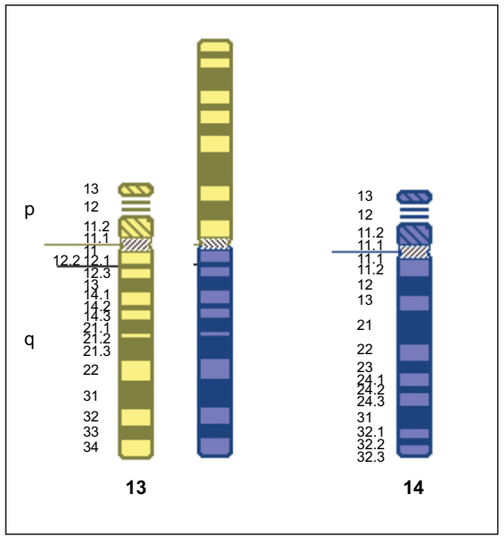

Figure 3 Robertsonian translocation

smaller the risk that the fetus will be viable if the karyotype is unbalanced[16].

Multiple miscarriages may occur in translocation carriers. Following three miscarriages it is recommended that a couple undergo chromosomal analysis to investigate the presence of a chromosomal abnormality (Figure 4).

Other chromosome abnormalities

Chromosome inversions

A segment of a chromosome may invert involving both the long and the short arms of the chromosome and this is known as a pericentric inversion. Depending on the position of the breaks on the chromosome this can have a reproductive risk for a pregnancy. If the breaks

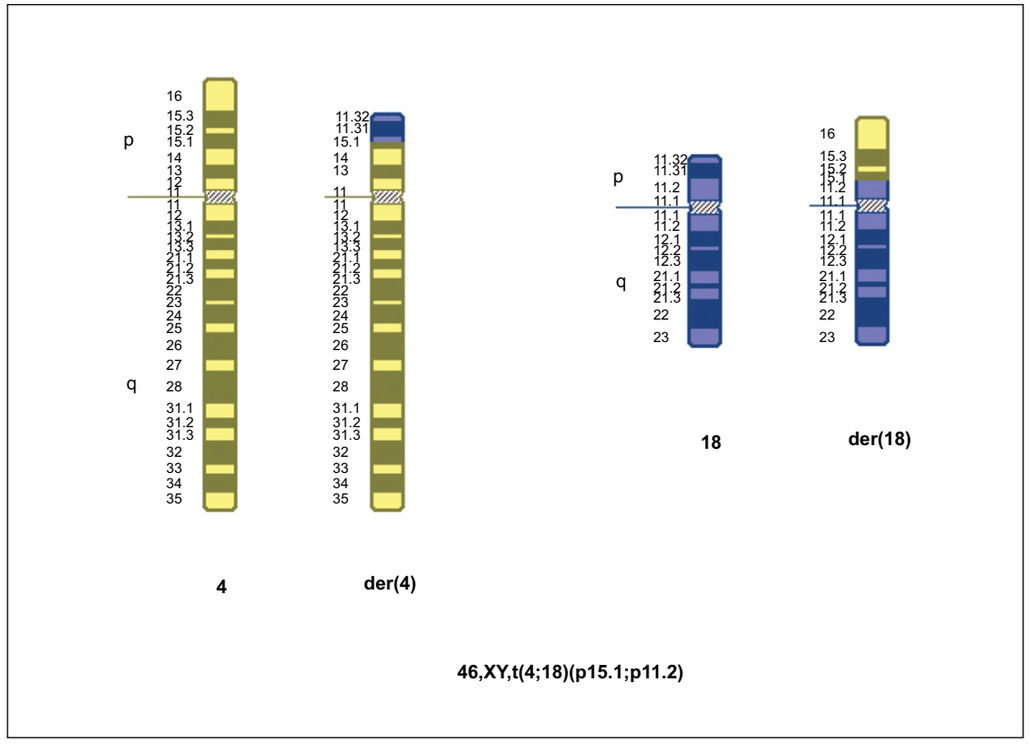

Figure 4 Balanced reciprocal translocation

are on the same side of the centromere, known as a paracentric inversion, the reproductive risks are very low (Figure 5).

Chromosome markers

Marker chromosomes are small extra parts of chromosomes that can cause major congenital abnormalities depending on the chromosomal origin. If a parent carries a marker and is unaffected, it is unlikely to cause problems in a baby. Chromosome markers can potentially reduce fertility and lead to imprinting defects. Marker chromosomes are frequently identified only in a proportion of cells (chromosome mosaicism, i.e. different groups of cells within an individual have a different chromosome makeup), as they are innately more unstable during mitoses and have a tendency to get lost during cell reproduction. If, however, the parent is a mosaic and the baby has the abnormality in every cell, there is a potential that there could be a phenotypic effect.

If a chromosome abnormality is suspected, the karyotype can be examined on blood chromosomes. If the abnormality is very small, it may only be recognized using fluorescence *in situ* hybridization (FISH); this would not be routinely undertaken. Molecular analysis does not identify balanced carriers and, therefore, is not a useful adjunct to cytogenetics. Small translocations cannot be identified by standard cytogenetics as they are beyond the resolution of the microscopes used. Methods of preparing chromosomes for analysis have improved over the past 15 years; therefore, a karyotype may need to be repeated if it was performed many years ago.

Preconceptional counseling considerations

It is necessary to assess the following points when considering a future pregnancy:

1. Is the couple at risk?
   a. What is the risk?
   b. What is the burden of the disease?
   c. Is preventative intervention possible?
2. What are the parents' expectations for a future pregnancy?
   a. Do they wish to avoid the birth of an affected baby by conventional prenatal diagnosis (CVS, amniocentesis, ultrasound)?
   b. Do they wish to investigate the possibility of preimplantation genetic diagnosis (PGD)?

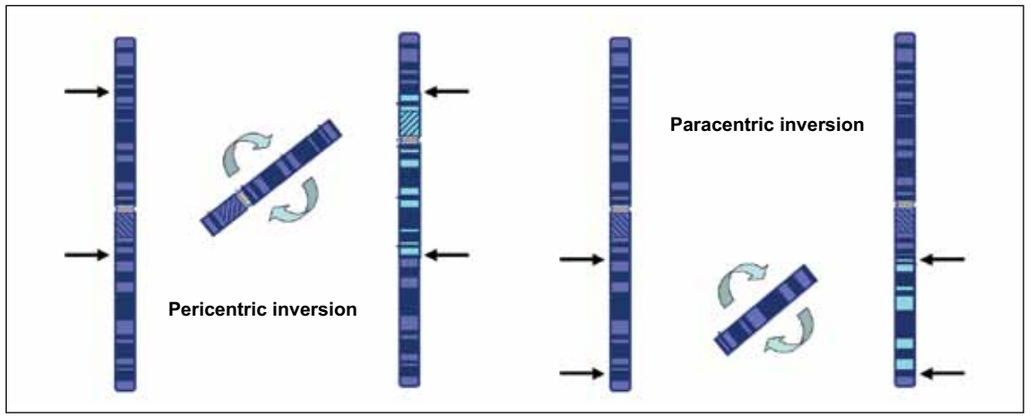

Figure 5 Chromosome inversions

   c. If no prenatal diagnosis is available, is the risk to future pregnancies known?
   d. If they would not consider having a pregnancy that might be affected and could not consider (a) or (b), then the available options are:
      i. Avoid further pregnancy;
      ii. Adoption;
      iii. Artificial insemination donor (AID)/ovum donation.

Preconceptional counseling is more preferable than counseling once a patient is pregnant, as information gathering and molecular testing may take a prolonged length of time resulting in:

1. Undue anxiety in pregnancies that may not be at risk;
2. Prenatal diagnosis not being available as test results are not obtainable;
3. Prenatal diagnosis being undertaken late;
4. Couples not having enough time to consider their options carefully.

Certain common disorders may be amenable to mass preconceptional screening such as sickle cell disease, thalassemia and cystic fibrosis. They are common genetic diseases with a high carrier frequency in specific populations. Screening for hemoglobinopathies is possible on a full blood count and screening for four mutations in the cystic fibrosis gene would pick up 75% of all carriers in the northern European population. Accessing the target population remains a challenge as on average 60% of pregnancies are unplanned, and uptake of this type of service is likely to be low. There are no preconceptional screening programs in the UK. Vaccination for rubella in the mumps, measles and rubella (MMR) vaccine is the only preventative measure undertaken in this group and this is at the age of 12 months!

Folic acid

It currently is recommended that all women take folic acid prior to as well as after conception. Spina bifida incidence has reduced since the recommendation of periconceptional folic acid and through the fortification of all wheat products in some countries such as the US, although the incidence of anomalies had already been falling especially in previously high risk areas. In couples who have already had a baby with spina bifida it is recommended that 5 mg daily is taken rather than the normal recommended daily dose of 0.4 mg. Folic acid is also said to reduce the recurrence risk of cleft lip and palate, and women with a previously affected pregnancy are also recommended to take 5 mg daily of folic acid.

GENETIC CAUSES OF INFERTILITY

A few couples presenting at infertility clinics have identifiable genetic causes for their infertility. Azoospermic men with congenital absence of the vas deferens should be tested for cystic fibrosis mutations which account for more than 50% of this group[17–19]. Azoospermic men should also have their karyotype examined, as Klinefelter syndrome, 47,XXY, is present in 1 : 500 men and is increasing in incidence for undetermined reasons. Y chromosome microdeletions can also cause azoospermia, and molecular or FISH analysis is likely required to identify these individuals. Intracytoplasmic sperm injection (ICSI) can be used in a proportion of men with azoospermia, but the cause of the infertility may then be passed on. In women, Turner's syndrome, 45,X/46,XX, may cause infertility. If these women succeed in conceiving, they have a higher incidence of chromosomally imbalanced offspring. Women with polycystic ovary syndrome may have a mild form of congenital adrenal hyperplasia which is amenable to treatment.

As chromosomal translocations may cause multiple miscarriages and infertility, karyotyping may be recommended. Clementini and colleagues[20] identified 3.95% of couples as carrying a chromosomal translocation in a study of patients referred for assisted reproduction. Many other disorders can also interfere with fertility, but it is beyond the scope of this chapter to consider them further.

MATERNAL HEALTH AND GENETIC DISEASE

With the improved prognosis of many childhood-onset diseases, many women who in the past would have either died or whose health would not have permitted a pregnancy now are able to consider a pregnancy. A number of issues need to be considered:

1. The fetus may be at risk of the same disease, as an autosomal dominant disease has a 1:2 chance of being passed to the fetus.
2. The disease process may affect the developing fetus.
3. Maternal health might be severely compromised by the pregnancy. Some diseases improve during the pregnancy only to deteriorate postnatally.
4. Maternal age for first pregnancy is increasing, and women may now have an illness in pregnancy that is rare in younger women, such as coronary artery disease.

Autosomal dominant diseases that may be inherited by the fetus and present *in utero*

All autosomal dominant diseases that affect one parent have a 50:50 chance of being passed on to the fetus. The disease may be of extremely variable severity, and the baby may be much more severely affected than the mother.

Myotonic dystrophy

Myotonic dystrophy affects approximately 1:5000 individuals. It can be asymptomatic for all of a patient's life, i.e. it is possible to be an asymptomatic carrier, or it can prove fatal in the neonatal period as a result of pulmonary hypoplasia and severe arythrogryposis. The congenital form is almost exclusively inherited from the mother. This disease exhibits anticipation. Classical myotonic dystrophy presents in early adult life with myotonia which is worse in the cold, facial diplegia, progressive muscular weakness, cataracts and extreme fatigue. Arrhythmias are common later on in the disease. It is slowly progressive, and the majority of patients show mental slowing with time. Both men and women have lower fertility with hypogonadotropic hypogonadism developing in men. Women who succeed in becoming pregnant have a higher risk of miscarriage and labor poorly with discordant uterine contractions resulting in a high rate of cesarean sections and postpartum hemorrhage. Anesthetics may cause malignant hyperthermia, and patients can have a prolonged recovery from anesthetic. All women affected with myotonic dystrophy should be carefully counseled regarding their own health and the risk to their fetus. Referral to specialized genetic counseling is strongly recommended[21].

Autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is a common cause of end-stage renal failure. It has an incidence of 1:400–1:1000[22] individuals. There may be no previous family history of the disease. Two genes have been discovered that cause the disease, PKD1 and PKD2, with 85% of cases being due to mutations in PKD1 and a milder phenotype in PKD2. Cysts do not normally occur until early

adult/late teenage years; however, presentation may occur *in utero*[23]. This may be the first presentation in the family and, in any fetus that is identified as having cystic kidney disease, both parents should have a renal ultrasound. The most common form of fetal severe renal cystic disease is autosomal recessive polycystic disease (ARPKD), which invariably leads to renal failure in childhood and is normally lethal at birth owing to oligohydramnios and pulmonary hypoplasia. If the diagnosis is ADPKD, the outcome for the baby is good with normal renal function in childhood to be expected. Careful management of the child's blood pressure and treatment of urinary tract infections prolongs renal function. Pregnant women with ADPKD are at increased risk of developing hypertension during pregnancy, and renal function needs to be monitored. If a couple have had one child with prenatal presentation of ADPKD and one of the parents is affected, then the recurrence risk for the *in utero* presentation is 1:4.

Marfan's syndrome

Marfan's syndrome has a prevalence of 1–5:10,000, the major physical features being tall stature with arrachynodactyly with an arm span 10% more than the height, high arched palate, scoliosis and stretch marks. The major complications are lens dislocation and dissecting thoracic aortic aneurysm. The latter is of concern during pregnancy, and it is necessary for affected women to have an echocardiogram prior to pregnancy to look for any aortic root dilatation that may dissect during pregnancy. Marfan's syndrome may be identified in the fetus on ultrasound but normally this is the neonatal form of the disease which, although due also to mutations in fibrillin 1, is normally a result of specific mutations which are lethal in childhood. Most cases of Marfan's syndrome would only be identified *in utero* by DNA analysis at CVS[24].

Ehlers-Danlos syndrome

Ehlers-Danlos syndrome (EDS) encompasses a large number of different genetic diseases with widely differing severity[25]. Ehlers syndrome type I which is associated with joint hypermobility, tall stature, hyperextensibility of the skin, easy bruising and cigarette paper scars can result in premature rupture of the membranes if the fetus is also affected due to weakness of the amniotic membranes. Repair of any tears/incisions after delivery should only be undertaken by an experienced surgeon as tissues are extremely friable.

Tuberous sclerosis

Tuberous sclerosis is a highly variable disorder due to mutations in two genes, TSC1 and TSC2. In its most severe form, it is associated with severe mental retardation and intractable fits; however, in its mildest form it may have only mild skin manifestations. The majority of affected patients have mild learning difficulties, well controlled epilepsy, some skin manifestations and possibly leiomyomata of the kidney. The patient may wish to undergo invasive prenatal diagnosis in view of the approximately 10% of cases that have the severe form of the disease, a mutation needs to have been identified within the gene in the family prior to the pregnancy for this to be feasible. A fetus may develop cardiac rhabdomyoma *in utero*. These rarely cause fetal/neonatal compromise and disappear over the first year of life but are an indication that the fetus is affected. An affected woman may be on antiepileptic drugs which may need to be changed prior to the onset of pregnancy.

MATERNAL GENETIC DISEASE THAT MAY BE AFFECTED BY PREGNANCY

Cardiac disease

Many women with successfully repaired congenital heart disease are now becoming pregnant. Most of these defects are unlikely to reoccur in the fetus, but careful assessment of the heart will be required both preconceptionally and during the pregnancy, as cardiac decompensation is not uncommon. Detailed cardiac examination of the fetus is often offered. Although the offspring risk is only of the order of 3.2%, the risk is higher if the mother rather than the father is affected[26].

Di George syndrome (velocardiofacial syndrome)

Di George syndrome is the commonest microdeletion syndrome. It is caused by a microdeletion on chromosome 22q11.2. Conotruncal cardiac defects are the commonest type of congenital heart disease. All couples where one parent is affected should be offered either prenatal diagnosis by CVS or detailed cardiac scanning. Other abnormalities include cleft palate, renal abnormalities, immune deficiency, short stature, mild to moderate mental retardation and hypocalcemia. Hypocalcemia needs to be screened for during or prior to every pregnancy as it can be asymptomatic, and the fetus, even in the absence of the deletion, may become hypocalcemia if the mother is hypocalcemia.

Cardiomyopathy

Hypertrophic cardiomyopathy Hypertrophic cardiomyopathy (HCM) is the commonest form of inherited cardiomyopathy with an incidence of 1:500[27]. Most adult-onset cases of HCM are inherited as autosomal dominant diseases with very variable penetrance. HCM is surprisingly well tolerated during pregnancy, with few patients with previous stable cardiac function deteriorating during pregnancy[28,29]; however, many women may be taking beta-blockers and a few will have implantable cardioverter defibrillators (ICDs). Children may be affected with HCM, but it is extremely unusual for a child to become symptomatic before the age of 8, even in the presence of hypertrophy that has been already identified.

Dilated cardiomyopathy The incidence of dilated cardiomyopathy has only been formally assessed by Codd and associates[29] in 1989. This study found the prevalence to be 1:2700; however, this was a gross underestimate. Dilated cardiomyopathy is thought to have a genetic basis in a less than 50% of cases; other causes include viral agents, drugs, radiation, coronary artery disease and hypertension. Decompensation is commoner in pregnancy than in HCM, and careful assessment needs to be undertaken prior to pregnancy. Labor needs to be particularly carefully monitored, and anticoagulation may be required. Patients with impaired cardiac function at the beginning of pregnancy are at the highest risk.

Arrhythmogenic right ventricular dysplasia The overall incidence of arrhythmogenic right ventricular dysplasia (ARVC) is about 1:5000. ARVC was only recognized in the 1990s, and it is a difficult diagnosis to confirm in the early stages as it requires cardiac magnetic resonance imaging and other specialist cardiac investigations[30]. Referral to a cardiologist specializing in inherited cardiac disease is advisable if the diagnosis is uncertain. Successful pregnancies have taken place in ARVC with the highest risk patients being those who have evidence of cardiac failure prior to the onset of the pregnancy.

Primary rhythm disorders

Long QT (LQT) syndromes are the most well recognized of this group with an overall incidence of 1:5000. The majority are inherited as an autosomal dominant trait, and the penetrance is highly variable. Pregnancy is a relatively safe time for patients with LQT syndrome, although severe hyperemesis can cause metabolic decompensation and should be treated more aggressively than in unaffected patients. Rashba and co-workers[31] undertook a retrospective study of cardiac events in LQT syndrome and compared prepregnancy, pregnancy and postpregnancy events of syncope, palpitations and sudden death. Of these patients, 2.8% had a cardiac event prepregnancy, 9% during pregnancy and 23.4% postpartum. Postpartum seems to be the most vulnerable time, especially in carriers of LQT2 mutations[32]. Many drugs (refer to CRY website[33] for up to date list) are contraindicated in LQT syndromes, and it is essential that these are not given to affected women as they may precipitate arrhythymia. Sleep deprivation may make patients more vulnerable to arrhythmias, and sudden waking from a deep sleep is a known risk factor in these disorders. Beta-blockers should be taken regularly during this period. There appears to be a small increase in the risk of sudden infant death syndrome in babies with LQT syndrome which may cause an increased amount of stress on the mother.

Other rhythm disturbances are even rarer and beyond the scope of this chapter, including Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT) and isolated ventricular tachycardia.

Hypercholesterolemia

Statins are contraindicated in pregnancy. Although systematic review of the teratogenic effects has not supported the initial reports, it is advisable for these agents to be stopped during pregnancy[34].

Ehlers Danlos syndrome type I

EDS type I is mentioned above regarding premature rupture of the membranes. EDS type IV (EDS IV) is probably the most dangerous genetic disease of all during pregnancy; it is caused by mutations in collagen III. It can be inherited as an autosomal dominant or recessive form, and affected patients can be recognized by their premature aged appearance. They are highly prone to vascular rupture of medium sized arteries, such as the cerebral arteries, resulting in subarachnoid hemorrhage, coronary artery dissection, and mesenteric artery and intestinal rupture. Mortality has been quoted as up to 30% during pregnancy, and therefore pregnancy should be discouraged.

Respiratory disease

Cystic fibrosis

Many women with cystic fibrosis are now of child-bearing age. Whereas men with cystic fibrosis are azoospermic, women are able to conceive naturally. The success of a pregnancy depends on appropriate management of maternal health. The safety of a pregnancy must be discussed with the patient's respiratory physician. It is advisable that the partner is tested for cystic fibrosis. The northern European population carrier frequency is 1:24, but in other parts of the world it is lower. Of the mutations in the northern European population, 90% can be screened.

Metabolic disease

Survival without mental retardation was rare in this group of diseases, but early management

means there are an increasing number of adults of reproductive age who may wish to consider a pregnancy. There are many metabolic diseases, and specialists in metabolic medicine should be consulted for optimum management.

Phenylketonuria

Women affected with phenylketonuria (PKU), but effectively treated in childhood, are now having their own children, although the risk of the child being affected with PKU is low as it is an autosomal recessive disease. A strict low phenylalanine diet needs to be followed preconceptionally to avoid mental handicap and microcephaly in the fetus. Poor maternal control of PKU also results in an increased risk of congenital heart disease.

Ornithine carbamoyltransferase deficiency

Ornithine carbamoyltransferase deficiency (OCT) is an X-linked disorder frequently lethal in early infancy in males if not recognized. It is a urea cycle defect resulting in hyperammonemia and hepatic encephalopathy. Carrier women may have a protein aversion and present with hyperammonemia during intercurrent illness[35]. The presentation in girls may be subtle and missed. Treatment consists of a low protein diet and arginine supplementation. The puerperium is particularly high risk for these women when the body is catabolic. Labor needs to be carefully managed with early fluid replacement. Prenatal diagnosis can be requested.

Skeletal dysplasia

Women with skeletal dysplasia are not at high risk during pregnancy, and no particular management needs to be considered preconceptionally. Very short women may become breathless during advancing pregnancy, and delivery may occasionally have to be expedited. Women with kyphoscoliosis may be at particular risk. Women with osteogenesis imperfecta do not seem to have a high risk of fracture during pregnancy, but associated deafness may deteriorate during pregnancy. Increased osteopenia may occur during the postnatal period. Cesarean section is common and may be advisable due to abnormalities of the pelvic anatomy. Anesthetic review should take place as a number of skeletal dysplasias are associated with atlanto-occipital instability. Spinal anesthesia is unlikely to be contraindicated but may be technically challenging. If both partners have a skeletal dysplasia and the baby inherits both diseases, this can result in a very severe/lethal skeletal dysplasia and prenatal diagnosis may need to be discussed.

NON-GENETIC MATERNAL DISEASE LEADING TO CONGENITAL ABNORMALITIES IN THE FETUS

Systemic lupus erythematosus

Systemic lupus erythematosus is covered in Chapter 7.

Diabetes mellitus (diabetic embryopathy)

Diabetes mellitus is the most common chronic illness in pregnant women. The incidence of both type 1 and 2 diabetes is increasing. Type 2 diabetes is becoming increasingly problematic in pregnancy due to increasing obesity and increasing maternal age – developments that are seen in most developed countries and many parts of the developing world. Preconceptional counseling for diabetic mothers is well recognized and does not need to be reiterated in this chapter (see Chapters 5 and 32). Diabetic embryopathy is closely related to maternal control of blood sugar. The congenital abnormalities described in infants of diabetic mothers are protean and include neural tube defects, congenital heart disease, renal abnormalities, caudal regression, hemifacial macrosomia and limb abnormalities[36].

Periconceptional counseling in women with learning difficulties

Many women with mild to moderate learning difficulties become pregnant and have children. It is vitally important that they have access to normal antenatal services and equally important that information be explained in simple terms, as often they will not be able to read or write, and this may not be obvious to the doctor or health professional. They also may have specific health needs secondary to the underlying diagnosis which need to be addressed, and the risk of the baby having a similar or more severe learning disability needs to be assessed. Referral to the local genetics service for such assessment may be required. For example, a number of X-linked disorders such as fragile X syndrome may have partial expression in a girl, whereas a boy could be much more severely affected and prenatal diagnosis will need to be discussed.

In more severe cases of learning disability, the patient may not be capable of looking after a baby, and family discussions and involvement of social services are entirely appropriate. It is also useful to have frank discussions with the parents or caregivers in cases of severe disability to attempt to determine whether the sexual activity that led to the pregnancy was consensual or forced and whether the patient has the capacity to protect herself against sexual predators who may meet with her. The partner may also have learning difficulties and details of the cause of his problems may also need to be investigated. It is important to address the care of the child postnatally.

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32

Malnutrition: an antecedent of diabetes?

Kinneret Tenenbaum-Gavish and Moshe Hod

INTRODUCTION

Almost 25 years ago, Barker and associates published their first reports regarding the association between reduced fetal growth and a number of conditions occurring later in life. Notably, these investigators looked at the relationships between infant birth weight and future ischemic heart disease[1–3]. Two disparate observations led to the creation of the 'Barker hypothesis': first, the relationship between neonatal mortality and low birth weight; and second, the higher rates of mortality from heart disease in economically disadvantaged areas compared to more prosperous regions. At the basis of Barker's theory lies the assumption that malnourishment during intrauterine life can cause a series of adaptive changes in the fetus and the placenta, changes which bring about new metabolic regulation that becomes apparent in adult life.

Later, Barker and Hales put forward the 'thrifty phenotype' theory[4] concerning the association between low birth weight and the development of type 2 diabetes. This theory connects poor fetal and early life nutrition and growth (which causes irreversible changes in insulin and glucose metabolism – namely reduced insulin secretion and increased insulin resistance), with adult life obesity and physical inactivity, to explain the increased risk for type 2 diabetes. At the beginning of the 21st century, Bateson and Barker published their 'developmental plasticity theory'[5]. This theory presumes that the fetus responds to the nutritional condition of the mother as an adaptive mechanism preparing it to best fit environmental conditions later in life. When these environmental conditions change rapidly, the fetus who later becomes an adult is exposed to a different environment than the one he or she experienced *in utero*. This early preconditioning may become harmful or have a damaging effect on the specific risk to develop a specific disease(s).

The preceding commentary, although exceedingly brief, opens the discussion of a topic which is currently of great interest within the medical profession, that is, the epidemiological association between the intrauterine environment and adult onset diseases. The multiple theories that have been set forth to explain this improbable relationship all aim to explain how different phenotypes can be achieved with a given genotype. The integrated discipline trying to weld all of these theories together to form a new specialty is currently known as developmental origins of health and disease (DOHaD), and this chapter is written from this perspective.

IS BIRTH WEIGHT A RELIABLE INDICATOR FOR FETAL NUTRITIONAL STATUS?

Low birth weight obviously may serve as an indicator of a disrupted intrauterine environment. The growing fetus clearly is dependent upon a complex fetomaternal interaction. This

sophisticated interface relies on several components: maternal nutritional intake, uterine blood supply and placental transfer mechanisms, all of which depend on the maternal metabolic and cardiovascular condition.

If maternal nutrient supply is inadequate for fetal requirements, the fetus reacts by redirecting blood flow to the brain, adrenal gland and heart at the expense of other tissues, as well as by changing the secretion of several hormones such as insulin-like growth factor 1 (IGF-1), leptin, insulin and stress hormones[6,7]. The fetus may also redirect resources from tissues like muscle or bones towards the accumulation of fatty tissue. This may affect fetal body composition in a myriad of ways, some of them unexpected. For instance, fingertip ridge count (in particular that of the 5th finger) is low in those whose prenatal life may have been suboptimal as a result of the Dutch famine during World War II or who were exposed to the Dutch famine during prenatal life. This finding is now thought to be an indicator of the risk for diabetes in adulthood[8].

It is important to note that although birth weight is an easily measured variable and is readily available when conducting epidemiological studies, it is not a true diagnostic marker of maternal nutrition but rather an indirect indicator. Moreover, several other determinants also influencing birth weight are not related to the nutritional status of the mother, such as fetal gender or ethnic background. Furthermore, birth weight is an insensitive indicator of the timing, extent and duration of exposure to nutritional deprivation. Some randomized controlled studies even fail to find a significant effect of maternal dietary supplements (protein or caloric) on birth weight[9], whereas others demonstrate only a mild effect[10]. Under these circumstances, birth weight should be viewed as an insensitive substitute for other, more accurate, anthropomorphic (abdominal, head circumference, etc.) or metabolic variables which are currently unavailable in retrospective and epidemiologic studies.

EVIDENCE FOR FETAL PROGRAMMING

The pivotal role of the maternal nutritional condition on intrauterine growth and development as well as on perinatal mortality has been recognized for decades and thoroughly investigated, as noted above. The Dutch famine studies (referring to the famine occurring during the winter of 1944–45 while World War II consumed Europe) described the association between maternal malnutrition (mainly during first and second trimester of pregnancy) and low birth weight[11]. These studies also demonstrated congruity between low birth weight and the occurrence of cardiovascular morbidity and mortality later on[12].

Barker[13] first described the relationship between infants with low birth weight and risk of cardiovascular and metabolic diseases (diabetes and osteoporosis) in adult life. This relationship strongly implies that maternal malnutrition is related to longstanding or even permanent changes in the phenotype of the offspring, since such changes would of necessity have to occur during critical periods of early development. This process is currently referred to as fetal programming.

Recent studies indicate that the deprivation of certain elements, such as vitamin B12 and folate[14,15] may be associated with increased adiposity and insulin resistance in offspring. In a similar sense, over-exposure to harmful substances such as cigarettes, nicotine and alcohol, as well as intrauterine stress, may also cause fetal growth restriction and thus may influence prenatal and childhood outcome. The Pune Maternal Nutrition Study (PMNS)[14,15] was a prospective observational study conducted near Pune, India. The mean birth weight of about 700 infants included in the cohort study was only 2.7 kg, and although the newborns were extremely short and thin,

the babies were relatively adipose. The Indian babies were small in all body measurements, the smallest being abdominal circumference (standard deviation (SD) score −2.38, 95% CI −2.48 to −2.29) and mid-arm circumference (SD −1.82, 95% CI −1.89 to −1.75), while the most preserved measurement was the subscapular skinfold thickness (SD −0.53, 95% CI −0.61 to −0.46). This indicates that small Indian babies have small abdominal viscera and low muscle mass, but preserve body fat[15].

It has also been shown that maternal plasma levels of several nutrients and fuel materials (glucose, cholesterol and triglycerides) correlated with neonatal birth size and adiposity, and that low maternal intake of B12 but high folate correlated with insulin resistance in the offspring[14]. These data all demonstrate that adaptive changes are possible in the fetus during nutritional deficit – redirecting resources towards accumulation of fatty tissue which may provide fuel for brain growth and/or immune function. Such findings highlight the fact that birth weight provides only a crude summary of fetal growth and fails to describe potentially important differences in the development of specific tissues.

EPIGENETIC PROCESSES

The embryo inherits a given set of genes from both parents. It draws upon its genetic milieu for continued development and growth. However, the intrauterine environment in which the embryo/fetus develops is much more than a mere receptacle that contains the fetus until it has sufficiently developed for independent life. It is an interactive vessel that may dictate the expression of the genes, and may create permanent changes in their function and therefore alter the development of the fetus' bodily systems[6,7]. Epigenetics is 'the study of heritable changes other than those in the DNA sequence'[16] – or in other words, epigenetics studies the process by which a given genotype evolves into specific individual phenotypes. This should be distinguished from changes occurring to the DNA sequence such as mutations or polymorphisms which are genetic in nature.

After establishing the epidemiologic relationship between maternal malnutrition and later risk for cardiovascular and metabolic morbidity in offspring, one should try to look into the assumed mechanism by which this change occurs. There are several suggested methods by which genes are modified in the epigenetic process: DNA methylation, histone modification (acetylation) and microRNAs. These epigenetic mechanisms may help to illustrate how cell differentiation (i.e. how cells with the same genotype differentiate into different tissues) occurs.

Methylation of cytosine in the promotor region of a gene causes silencing of gene expression. Folate and B12 are important methyl donors. Animal models have demonstrated that maternal diet during pregnancy may influence the degree of methylation of specific fetal genes[17,18], affecting fetal and placental development. An experimental mouse model[17,19] showed that when pregnant mice were fed with a diet supplemented with methyl donors there was an increase in the coat-color gene methylation, and that a soy-rich diet caused increased methylation and reduced obesity in offspring. This means that the offspring, although sharing the same coat-color genes as its parents, had a distinctively different phenotype than its ancestors. There is some indication from plants that epigenetic changes can also be passed between generations of a species[20].

The growing fetus shows a remarkable ability to assume different sizes and discrete functional abilities within a given genotype. This trait has been referred to as 'developmental plasticity'[5]. It has been suggested that fetal programming limits the fetus's developmental plasticity and suppresses its ability to adapt effectively to the changing environment[21].

A more detailed and accurate understanding of the mechanism, by which maternal malnutrition influences fetal intrauterine growth, can be extracted from experimental and animal studies. Such suggested mechanisms include:

1. Simple growth failure: a reduction in size and number of cells in specific tissues, for example, a reduction in pancreatic beta cell mass or in the number of renal nephrons.
2. Alteration in endocrine settings: up-regulation of the hypothalamo–pituitary–adrenal (HPA) 'stress' axis and changed secretion and sensitivity to insulin and IGF-1.
3. Changes in the expression and regulation of DNA.

Intrauterine growth restriction (IUGR) is the end result of many conditions which influence the intrauterine and genetic environment inflicted upon the embryo/fetus. It is beyond the scope of this discussion to encompass the full range of the various maternal manipulations leading to IUGR in the offspring. It is sufficient to state that fetal growth and development depends upon an intricate relationship between maternal supply of nutrients and fetal-placental uptake. Animal models show that fetal growth can be restricted by reducing maternal caloric and protein uptake during pregnancy[22]. This effect has also been demonstrated in humans – mainly in the so called 'Famine studies'[23]. This effect is partly explained by simple deficiency of 'building materials', such as the observed low bone mineral content in children whose mothers suffered from low calcium intake during pregnancy[24], but it is clear that more subtle aspects of this issue await future investigation.

THE ASSOCIATION BETWEEN NUTRITION, MALNUTRITION AND DIABETES

The relationship between IUGR and diabetes or metabolic syndrome is much more complex. Intrauterine exposure to IUGR may be responsible for changes in fat distribution as described in the PMNS[14,15]. Later life obesity is potentiated by alterations in appetite regulation, and by increased adipogenesis. In a similar fashion, hypertension is made more likely by alterations in renal and blood vessel development, while diabetes is associated with alterations in cellular insulin signaling and decreased beta cell function. IUGR is associated with both anatomic changes in the pancreatic islets and with changes in intracellular insulin signaling pathways. The end result of these alterations is a decrease in the individual's capacity to secrete insulin, while at the same time there is an increasing demand for insulin leading to an increased likelihood of frank glucose intolerance[25].

These combined programmatic alterations induce the full metabolic syndrome in the adult. Fetal growth patterns are not the sole contributor to the development of type 2 diabetes. Patterns of childhood weight gain may have a crucial role in the rapidly rising prevalence of type 2 diabetes worldwide. This is owing to what has been referred to as the 'nutritional transition' (increased availability of food, reduced physical activity and increases in obesity). Not surprisingly, urban populations in developed countries, in which nutritional transition is more apparent, manifest the greatest rise in incidence of diabetes[26]. Those who were born small for age and later become overweight are at the highest risk for type 2 diabetes[27–31]. In other words, *adults with impaired glucose tolerance or diabetes tend to be, as a group, overweight. They were not, however, overweight as neonates, rather, they became overweight as a result of an accelerated gain in body mass starting in early childhood. The ability of children to have an accelerated increase in body mass may be a recent phenomenon in developing countries, a consequence of nutritional transition* (Figure 1).

Bhargava *et al*.[26] conducted a longitudinal study of 1400 adults who grew up in Delhi, India, at a time of rapid nutritional transition.

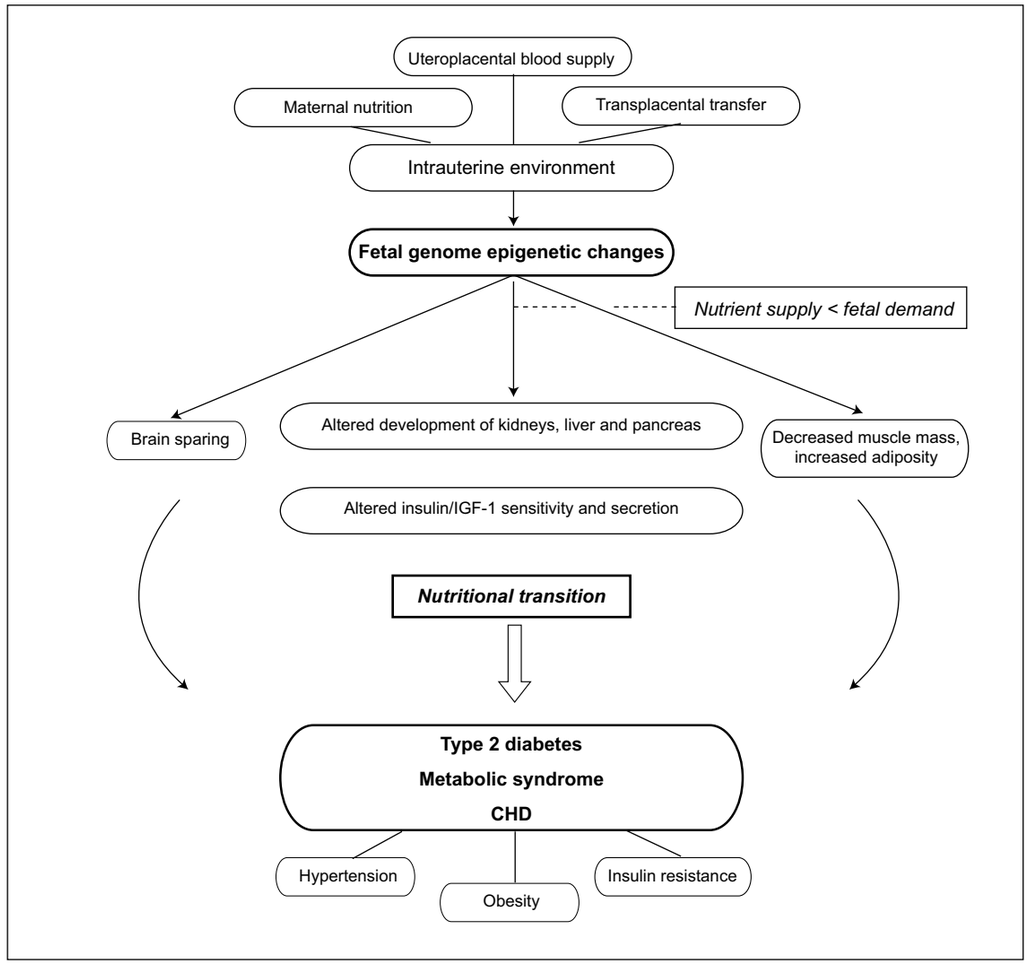

Figure 1 Factors affecting nutritional transition. IGF, insulin-like growth factor; CHD, coronary heart disease

These investigators found that a small size at birth, defined by a low birth weight or ponderal index, was associated with increased plasma glucose and insulin concentrations, and insulin resistance during adulthood.

At the age of 30 years, 15.2% of the study group had impaired glucose tolerance or diabetes, and 4.4% had diabetes. Serial standard glucose tolerance tests showed a sharp deterioration in glucose homeostasis at a relatively young age in adult life[26]. The growth of children in whom impaired glucose tolerance or diabetes later developed was characterized by a low body mass index (BMI) between birth and 2 years of age, a young age at adiposity rebound (as defined by the age after infancy at which the BMI starts to rise), and a sustained accelerated gain in BMI until adulthood.

Childhood obesity was uncommon among 8760 boys and girls who grew up in Helsinki, Finland, during World War II, affecting only 0.4% at the age of 12 years[32]. A total of 290 children in that study developed type 2 diabetes in adult life. They were all small for age at

birth, and all had low weight at 1 year of age. Their mean BMI did not exceed the average for the cohort until the age of 5 years. Thereafter, they had an early adiposity rebound and an accelerated gain in weight and BMI, but not in height. In that study, the prevalence of type 2 diabetes fell progressively from 8.6% in individuals whose adiposity rebound occurred before the age of 5 years to 1.8% in those in whom it occurred after 7 years. Despite these seemingly related findings, it remains unclear which is the most crucial phase during childhood and early adulthood during which excessive weight gain increases most the risk for adult type 2 diabetes.

The increase in prevalence of diabetes is of concern, not only as a healthcare burden on individuals and economies worldwide, but also owing to its effect on the next generations. Multiple studies have helped imprint the concept of hyperglycemia during pregnancy as representing a menacing epidemic in many parts of the world[33]. This spreading ailment carries grave short- and long-term consequences for both mother and child.

Diabetes affects the metabolism of all nutrient components (carbohydrates, fatty acids and proteins), of which glucose is the most prominent. Poor metabolic control may also induce alterations in levels of fatty and amino acids. Glucose and those other metabolites may account for the multitude of pathologies inflicted upon the offspring of a diabetic mother. These pathologic conditions range from congenital malformations and intrauterine fetal death to macrosomia, respiratory distress and hyperbilirubinemia. This creates an altered environment in which the embryo and fetus of the diabetic mother may be exposed to changes in gene expression and increased teratogensis[34,35]. Pederson *et al.*[36,37] and Salvesen *et al.*[38,39] observed the relationship between maternal hyperglycemia, fetal hyperglycemia and hyperinsulinemia. Insulin has an anabolic effect on muscle and adipose tissue linked to fetal macrosomia. On the other hand, long standing diabetes has a detrimental effect on the maternal vascular bed and its uteroplacental blood supply, and thus is linked to IUGR.

Follow-up studies, such as those conducted by Krishnaveni *et al.*[40] and Dabelea *et al.*[41], show that infants of diabetic mothers are at increased risk of obesity and glucose intolerance as early as age 5[40]. *Most importantly, intrauterine exposure to diabetes* per se *conveys a high risk for the development of diabetes and obesity in offspring in excess of the risk attributable to genetic factors alone*[41]. A Danish study[42] also demonstrated high prevalence of type 2 diabetes or pre-diabetes among 597 adults exposed to a hyperglycemic intrauterine environment. More than 20% of offspring born to mothers with diet-treated gestational diabetes mellitus (GDM) and more than 10% of offspring born to mothers with type 1 diabetes had type 2 diabetes or pre-diabetes at the age of 22 years. Compared with offspring from the background population, the adjusted risks of type 2 diabetes/pre-diabetes were increased eight- and fourfold, respectively[42].

These findings are apparently not in agreement with the previously explained theory associating IUGR and later risk for diabetes. They may, however, emphasize two aspects of the same issue, the manner in which intrauterine environmental conditions determine future risks of disease expressed in adult life, which then become the basis of fetal programming.

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33

Who should provide preconceptional care?

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INTRODUCTION

The simple answer to the question of 'Who should provide preconceptional care?' is that there is a role for every healthcare professional who comes into contact with any woman of childbearing age to provide appropriate information, support and care that relates to the specific needs and desires of the woman. In the UK, much preconceptional care for women with established medical conditions which impact upon pregnancy (e.g. diabetes, epilepsy, renal disease, etc.) has traditionally been viewed as the responsibility of the secondary service providing care for the underlying medical condition. However, as many pregnancies are not 'planned' and women may not be attending secondary care for regular follow-up, it is vital that preconception information and support be seen as everyone's responsibility.

TRADITIONAL PRECONCEPTIONAL CARE MODEL WITH DIABETES AS THE EXAMPLE

It is well known that women with type 1 and type 2 diabetes have an increased risk of adverse pregnancy outcomes, including miscarriage, fetal congenital anomaly and perinatal death[1] (see Chapter 5). There is a significant relationship between adverse outcome of pregnancy and poor glycemic control in early pregnancy in women with type 1 diabetes, with a fourfold increase in adverse outcomes, a fourfold increase in spontaneous abortion and a ninefold increase in major malformation in women with a glycated hemoglobin (HBA1c) above 7.5% at booking in one UK study[2]. At the same time, the infants of women with type 1 diabetes who attend multidisciplinary prepregnancy counseling show significantly fewer major congenital malformations compared to infants of non-attending mothers[3]. The 2005 CEMACH found that only 38.2% of women with type 1 diabetes had prepregnancy counseling documented in their notes and that a similar number (40%) had a prepregnancy glycemic test[4]. Other disturbing results in this report included an association between poor pregnancy outcome and unplanned pregnancy (odds ratio (OR) 1.8), and no contraceptive use in the 12 months prior to pregnancy (OR 2.3) with 40% of women with type 1 diabetes not planning their last pregnancy[1].

Prepregnancy counseling clinics have been traditionally been provided by adult diabetes services in secondary care. These clinics are usually staffed by diabetes specialist nurses (DSNs) and midwives. Women routinely followed up in the adult secondary care diabetes services should be receiving general preconceptional advice *when they attend for regular review of their diabetes* and be referred for more detailed preconceptional counseling and care at the prepregnancy clinic when they say that they are contemplating pregnancy.

Given that we know that when diabetes is in good glycemic control at the time of conception the risk of adverse outcomes is reduced,

that attending a preconceptional counseling clinic diminishes adverse outcomes, and that planning a pregnancy is associated with better outcomes, it is logical to ask why only 40% of pregnancies in women with diabetes are reported as being planned and only 38% have prepregnancy counseling documented in their notes?

WEAKNESSES IN THE TRADITIONAL SECONDARY CARE MODEL OF PRECONCEPTION CLINICS

First and foremost, all parties concerned must recognize that the majority of pregnancies are unplanned. The dichotomy between 'planned' and 'unplanned' pregnancy is a concept widely recognized in health policy and health service provision, but it has long been recognized as being problematic[5]. The reason that it is 'problematic' is the fact that this arbitrary and conventional division often fails to reflect the myriad of reasons that constitute the background to women becoming pregnant[6]. In a qualitative study of 15 women with type 1 diabetes who described 40 pregnancies, a positive step towards becoming pregnant was taken in 23 pregnancies but not in the remaining 17[5]. This study suggested that the intention to become pregnant needs to be considered as a continuum between planned and unplanned, with the majority of pregnancies falling somewhere in between planned and unplanned. The study concluded that formal preconception clinic sessions are unlikely to have an impact on most pregnancies for women, as attendance *assumes* some prior consideration of becoming pregnant[5].

Second, preconception clinics may actually cause anxiety in some attendees and thus discourage attendance. In the qualitative study cited above, three women (out of the 15 with type 1 diabetes interviewed) described attending preconceptional counseling and the anxiety it provoked. All three spoke about the fear they experienced after attending preconceptional counseling and that after attendance they found it difficult to make the decision to become pregnant. Clearly, the risks of pregnancy to the women and the baby need to be explained, but this information can lead to anxiety and fear. More research is needed to assess the potential for unintended adverse effects of preconceptional counseling on women's psychological wellbeing, and methods found to provide accurate and helpful information to women without inducing anxiety and fear.

Third, many women are being diagnosed with type 2 diabetes in childbearing age (often due to obesity), and such women may be being looked after exclusively in primary care. In fact, in some areas of the world there are as many women with type 2 diabetes becoming pregnant as there are women with type 1 diabetes, a huge difference from the situation 20 or so years ago, when pregnancy in diabetes was almost exclusively in women with type 1 diabetes. If women of childbearing age with type 2 diabetes are not being seen in secondary care, as is usual in many parts of the UK, they may not get referred into the secondary care-based preconceptional counseling clinics.

THE ROLE OF PRIMARY CARE IN PRECONCEPTIONAL CARE

Primary care is in contact with women with pre-existing medical conditions who will benefit from preconception information, advice and care, through the provision of contraception, the prescription of repeat medications, and the treatment of acute illness. These contacts may be with a general practitioner (GP) or practice nurse. All such interactions can be used to reinforce important preconception information. It is important to have enough time in the consultation to give important preconception messages and to realize that it is important to take every opportunity to do so.

THE ROLE OF THE QUALITY AND OUTCOMES FRAMEWORK IN INCENTIVIZING PRIMARY CARE

The quality and outcomes framework (QoF) is a 'pay for performance' initiative that was introduced on 1 April 2004 as part of the new GP contract. It linked part of a GP's income to the achievement of levels of process and intermediate outcome measures in 10 clinical areas. Achievement in these areas earns 'points' and points translate into income for the practice.

Pay for performance initiatives have been introduced in a number of countries in the world, but the QoF in the UK is the best developed and is the only one that publishes data on virtually all practices from every part of the country. Information from the QoF is published annually on the NHS information centre website[7] and is freely available to all, providing data at national, regional, primary care trust and practice level.

In the clinical area of diabetes, measures of process of care (e.g. recording of weight, blood pressure and appropriate blood tests) and measures of intermediate outcomes of care (e.g. having good glycemic control as defined by a specific HBA1c level and good blood pressure control defined as a blood pressure at or below 140/80 mmHg) have shown increases year on year from 2004 to 2008. Outcomes such as those cited indicate that pay for performance measures in QoF have had value in incentivizing primary care to deliver defined process and intermediate outcomes. Given these facts, it may therefore be possible to encourage primary care to take on a role in delivering preconception information, support and care through the development of suitable QoF clinical indicators. In diabetes, such a new clinical indicator for QoF has been proposed for consideration (Dornhorst A, Pierce M, Gadsby R, personal communication August 2010). It said something along the lines of 'all women of childbearing age who are living with diabetes should have a record in their notes of a discussion about preconceptional care issues at each annual diabetes review'. This proposed new indicator has been put into the National Institute for Health and Clinical Excellence (NICE) QoF clinical indicator development process for consideration in the 2011/2012 round.

THE ROLE OF NICE IN ENCOURAGING INVOLVEMENT IN PRECONCEPTIONAL CARE

In the UK NICE produces guidelines on specific conditions. These guidelines contain recommendations that, although they are not technically mandatory for implementation, do provide clear statements of good practice that should be followed.

In 2008 NICE published its first guideline on Diabetes in Pregnancy[8]. It contains an entire chapter on preconceptional care with an extensive literature review of the subject and a series of recommendations which include:

- Guideline Recommendation 1.1.8.1 – Women with diabetes should be informed about the benefits of preconception glycemic control at each contact with health care professionals, including their diabetes care team, from adolescence
- Guideline Recommendation 1.1.8.2 – The intentions of women with diabetes regarding pregnancy and contraceptive use should be documented at each contact with their diabetes care team
- Guideline Recommendation 1.1.2.1 – The importance of avoiding unplanned pregnancy should be an essential component of diabetes education from adolescence for women with diabetes.

The guideline also lists information about how diabetes affects pregnancy and how pregnancy affects diabetes. This is valuable information that needs to be conveyed to women with diabetes who are planning to become pregnant. If

these recommendations were carried out, they could play a significant part in reducing the adverse outcomes that are at present seen in the pregnancies women with diabetes.

SUMMARY AND CONCLUSION

In the UK, preconceptional care for women with pre-existing medical conditions that can affect pregnancy has usually been undertaken by the secondary care service looking after the particular medical condition.

Using diabetes as an example, it is apparent that less than 50% of women actually receive prepregnancy counseling in secondary care for a variety of reasons.

The concept is advanced that every healthcare professional consultation with such women should be used to convey preconception messages, including the importance of involving primary care teams.

Better primary care involvement in preconceptional counseling among diabetics in the UK could be incentivized using the quality and outcomes framework.

Recommendations from NICE guidelines provide clear statements of good practice that should be followed.

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Index